Heart and lung function in the critically ill and the effect of fluid loading

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ACADEMISCH PROEFSCHRIFT

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‘La dernière démarche de la raison est de reconnaître qu'il y a une infinité de choses qui la surpassent. Elle n’est que faible si elle ne va jusqu’à connaître cela.’

Uit: ‘Les Pensées’, fragment 177, Blaise Pascal

CONTENTS

CHAPTER 1

INTRODUCTION

FIRST PART: Pulmonary dysfunction in the critically ill

In critically ill patients, respiratory problems are common and complicate the course of the disease. Among other diseases, this has been described in septic patients (1,2), trauma patients (3,4) and in patients after cardiac and aortic surgery (5-8). These conditions are associated with an elevated risk of developing acute lung injury (ALI) or Adult Respiratory Distress Syndrome (ARDS). ALI and ARDS are characterized by severe arterial hypoxemia, a reduction of lung compliance and bilateral diffuse alveolar infiltrations on the chest X-ray. First, the diagnosis of both conditions is defined by the American-European Consensus Conference (AECC) criteria. According to these criteria, the diagnosis of ALI includes the presence of a P_aO_2/F_iO_2 gradient < 300 and the diagnosis of ARDS a P_aO_2/F_iO_2 gradient < 200 mm Hg, regardless of the positive end-expiratory pressure (PEEP), together with the presence of bilateral infiltrations on the chest radiograph. Furthermore, a pulmonary capillary wedge pressure (PCWP) <18 mm Hg and the absence of left atrial hypertension are necessary to exclude pulmonary dysfunction resulting from cardiogenic pulmonary edema, associated with increases in hydrostatic pressures (9). Second, the so-called lung injury score (LIS) incorporates gas exchange, radiological and lung mechanical abnormalities by taking the level of PEEP into account, together with the lung compliance being calculated as tidal volume/(plateau pressure-PEEP), the P_aO_2/F_iO_2 gradient and radiographic findings (number of quadrants with alveolar opacities). The LIS score ranges between 0 and 4, with values above 2.5 indicative of ARDS and between 0 and 2.5 of ALI (10).

Microvascular permeability

Injury of the alveolar-capillary membrane is a hallmark of ARDS, leading to increased permeability (11). Indeed, the presence of risk factors for developing ARDS is associated with increases in microvascular permeability (5,8,12-19), as well as the presence of pulmonary edema (20-24). Techniques for the measurement of endothelial permeability include the measurement of the flux of radiolabelled proteins between the intra- and extravascular compartment, for instance ^{67}Gallium (Ga) binding to transferrin (12-19). The so-called pulmonary leak index (PLI) has been

demonstrated to be specific and sensitive for an increase in pulmonary endothelial injury, associated with the presence of ALI and ARDS (12-14,18) and to be a valuable tool in the differential diagnosis between cardiogenic pulmonary edema and non-cardiogenic edema (14), two conditions with different treatments. However, the precise contribution of increased microvascular permeability to the genesis of lung edema in these patients has not been established and the PLI may be normal in some patients with ALI or ARDS (1). Some studies using PET-scan to evaluate extravascular densities as a measure of EVLW, in relation to microvascular permeability, which was measured as the pulmonary transcapillary ^{68}Ga-transferrin escape rate, did not find a relationship between both variables (25-27). Moreover, microvascular permeability was found to inversely correlate with gas exchange in some studies (4,28), but not in others (5).

Radiological consolidations and the detection of pulmonary edema

Chest opacities can be evaluated with either computed tomography (CT) scanning or chest X-rays. Possible causes of opacities include atelectasis and lung edema. Atelectasis is a common finding in up to 50% of the patients at risk for ARDS and contributes to radiographic abnormalities (7,29-32). Gas exchange abnormalities resulting from atelectasis may be difficult to differentiate from a fall in oxygenation resulting from increased permeability and pulmonary edema. This may be of importance, as the former may benefit from recruitment maneuvers, in contrast to the latter (33,34). However, radiological detection and particularly chest X-ray, have been shown to be insensitive for the accumulation of extravascular lung water (EVLW) or to detect changes in EVLW (24,35-39). In conclusion, both CT scanning and chest X-ray are of limited value in differentiating the primary cause of chest opacities, i.e. lung edema, atelectasis or pleural effusions (24,35,36,38-40). Moreover, transporting a patient in unstable conditions to perform a CT-scan is often not feasible.

Another possibility of measuring extravascular lung water, as a measurement of lung edema, includes the thermal-dye dilution technique (36,41-45), which consists of injecting ice-cold indocyanine green (= intravascular tracer) through the central

venous catheter with concomitant detection in the femoral artery. The dilution curves of both tracers are obtained, allowing calculation of the extravascular thermal volume, as an estimate of the EVLW (45). However, whereas radiography evaluates lung densities independently from the pulmonary blood flow, the measurement of the thermal-dye EVLW may depend on blood flow and therefore may underestimate pulmonary edema in the presence of pulmonary embolism or direct lung injury, associated with perfusion deficits (21,46-49). Furthermore, if the presence of EVLW with help of the thermal-dye technique is established, the consequences in terms of a disturbed gas exchange are far from resolved. A relationship between EVLW and gas exchange disturbances has been found in some studies (23), but not in others (41,42).

In conclusion, pulmonary dysfunction in patients at risk for ALI or ARDS includes a compromised gas exchange, lung mechanical and radiological abnormalities. These abnormalities can be explained by either increases in pulmonary microvascular permeability and the development of lung edema or the presence of atelectatic areas. Although risk factors for changes in pulmonary function in patients at risk for ARDS have been identified, the incidence and interrelation of these pulmonary abnormalities is unclear.

OBJECTIVES AND OUTLINES

In the first part of our thesis, we studied the incidence and pathogenesis of pulmonary ventilatory and radiographic abnormalities in three subsets of patients at risk for developing ALI and ARDS, i.e. post-operative cardiac surgery patients, aortic surgery patients and septic patients.

Cardiac surgery is a risk factor for post-operative pulmonary complications, associated with a compromised oxygen diffusion (7,50) and the occurrence of ARDS (incidence 0.4%) at the end of the spectrum, increasing the incidence of mortality in cardiac surgery patients from 5% up to 15% (51,52). First, an inflammatory response was shown to increase pulmonary microvascular permeability in some studies (5,12), but

not in others (53). Second, the use of cardiopulmonary bypass may be associated with increases in extravascular lung water (20,22), but this was not confirmed by other studies (36,54). Finally, mechanical conditions may be confounding factors in evaluating gas exchange, i.e. pleural lesions, sternotomy, harvest of mammary arteries, muscle paralysis, changes in compliance and anesthesia may cause disturbances of respiratory mechanics (22,32,55-58). Taken together, both the incidence and interrelation of the different manifestations of pulmonary injury is unclear in post-operative cardiac surgery patients.

In **chapter 2** we evaluated the occurrence and causes of pulmonary edema in mechanically ventilated patients within three hours after cardiac surgery involving cardiopulmonary bypass. In all patients we measured EVLW, capillary permeability, gas exchange, radiographic and ventilatory parameters.

Like cardiac surgery, aortic surgery is known to be complicated by impaired gas exchange and prolonged mechanical ventilation, associated with an increased mortality (6,8,59,60). In a previous study, we have demonstrated the importance of aortic clamping in the pathogenesis of endothelial injury, as aortic surgery with clamping was associated with an increase in pulmonary microvascular permeability, in contrast to peripheral vascular surgery (13,18). This type of surgery generates pulmonary injury, including ischemia/reperfusion injury, related to the clamping and unclamping of the aorta causing a systemic inflammatory response which results in neutrophil accumulation and upregulation of adhesion molecules leading to increased microvascular permeability (6,8,13,18,61). However, after major vascular surgery, mechanical factors may contribute to pulmonary dysfunction, e.g., as a result of a compromised chest compliance (59,60). Insight in the interrelations of pulmonary abnormalities in these patients can help to design therapeutic measures to better prevent pulmonary dysfunction.

In **chapter 3** we studied the mechanisms of pulmonary ventilatory abnormalities in relation to EVLW and capillary permeability in patients after major vascular surgery and ischemia/reperfusion.

In sepsis, known to be a major risk factor for ALI/ARDS, acute lung injury progressing to ARDS, can result from pneumonia or extrapulmonary causes. The degree of pulmonary dysfunction and lung injury, being of pulmonary (direct) or extrapulmonary (indirect) origin, may depend on the etiology and even may represent two distinct entities (33). The primary origin possibly predicts the effectiveness of treatment. In some studies, indirect forms of ARDS were associated with alveolar collapse and atelectasis, and thus may benefit from recruitment maneuvers, in contrast to direct forms of ARDS, associated with alveolar and lobar consolidations (33,62). Others however, claimed that the benefit of alveolar recruitment was less dependent on the cause of ARDS than the morphological abnormalities on CT scanning (63). Taken together, pulmonary or extrapulmonary causes of ARDS may differ in the degree of pulmonary injury and this distinction may have important therapeutic consequences.

In **chapter 4**, we studied the relation between gas exchange abnormalities and increased permeability edema in sepsis-associated acute lung injury/acute respiratory distress syndrome (ALI/ARDS) by pneumonia or an extrapulmonary origin.

SECOND PART: Fluid loading in the critically ill

Hypovolemia is relatively common after major surgery, including cardiac and vascular surgery, and is associated with major fluid shifts and hypotension (64-66). Fluid loading is the mainstay of treatment and goal-directed fluid therapy may even reduce intensive care unit and hospital lengths of stay (66). Different infusion fluids, crystalloids and/or colloids can be used to treat hypovolemia and are described in several reviews. These fluids may differ with respect to osmolarity, molecular weight and substitution, dispersion, metabolism, intravascular persistence and consequent plasma volume expansion (67-69). The colloid-crystalloid controversy refers to the ongoing debate on the relative merits and detriments of resuscitation from hypovolemia with infusion of either colloids or crystalloids. Meta-analyses suggest no beneficial or even a detrimental effect of colloids versus crystalloids (70-74). Furthermore, a recent meta-analysis suggested an increase in mortality, associated

with the use of albumin (75). However, these conclusions were heavily criticized by others (76). Potential detrimental consequences of resuscitation include intravascular volume overload, pulmonary edema, increased myocardial water content, gastrointestinal ischemia and systemic edema (77).

One of the major issues in the crystalloid-colloid controversy is the importance of the plasma colloid osmotic pressure (COP). The COP will be maintained or may even increase by the infusion of colloids and will be lowered by the infusion of crystalloids. It is unclear whether an increase in COP, associated with the infusion of colloids is accompanied by a greater speed and extent of plasma volume restoration as compared to crystalloids. Furthermore, the relative risks of fluid types to evoke pulmonary edema is unknown. By maintaining the COP, in contrast to crystalloids, colloids would prevent the development of pulmonary edema (72-74). However, possible side effects are disfavoring the use of colloids, including coagulopathies or anaphylactoid reactions and transmission of viral diseases (78,79).

Myocardial function and the effect of fluids

In clinical practice, volume status is frequently evaluated by measuring filling pressures, for instance the pulmonary capillary wedge pressure (PCWP) or central venous pressure (CVP) (80). These pressures however, are not very specific to assess preload or the volume expanding effect of fluid infusion. Indeed, filling pressures depend on blood volume, but also on vascular contractility, and myocardial function. Direct blood volume measurements, including intrathoracic blood volume index (ITBVI) and global end-diastolic volume index (GEDVI), are supposed to be better indicators of volume status, but not often used in clinical practice (45,81-83). Crystalloids and colloids often have been compared in their effects on cardiac output, most studies using filling pressures as endpoints of resuscitation. Some studies suggested for a given rise in filling pressure, no differences in the effect on cardiac output between fluid types (84-86), although higher volumes of crystalloids were needed to achieve the study endpoint. The ratio of crystalloid to colloid fluid volume to restore and maintain intravascular filling varied between 1 and 5 (74,85-91). However, other studies demonstrated differences in

fluid responses between resuscitation fluids, colloids resulting in a higher cardiac index (CI) for a given increase in filling pressures as compared to crystalloid, suggesting differences in cardiac contractility (92,93). Some studies comparing artificial colloids with albumin even suggested better myocardial performance with artificial colloids as compared to resuscitation with albumin (94-96).

Fluids may interfere with cardiac performance, independently from plasma volume expansion and increases in preload. Colloids were shown to decrease endothelial swelling and myocardial parenchymal injury (86) and to reduce myocardial ischemia/reperfusion injury (97). Furthermore, albumin was described to have a negative inotropic effect in injured patients (98), but a positive inotropic effect in cardiac surgery patients (99). Finally, in animal models of cardiac surgery, several studies suggest that the type of prime solution affects the amount of myocardial edema (100-103), which may influence left ventricular compliance and performance.

Fluids and pulmonary function

Plasma volume expansion and myocardial dysfunction may increase hydrostatic pressures in the pulmonary circulation, favoring fluid filtration and ultimately leading to interstitial lung edema and impaired gas exchange. Furthermore, an increase in microvascular permeability, as found in patients after cardiac or vascular surgery (12,13,18), decreases the gradient in COP between the intravascular and interstitial compartment. This gradient may be important in preventing the genesis of pulmonary edema. Colloids and crystalloids have been compared in their effects on pulmonary function, without finding differences as measured by shunting and/or gas exchange in patients with severe pulmonary insufficiency (104), after vascular surgery (88) or cardiac surgery (105). Direct measurements of EVLW however, with help of the thermal-dye dilution technique for instance, are scarce. In cardiac surgery patients, crystalloids and colloids used as prime solutions for cardiopulmonary bypass (CPB) were shown to affect EVLW differently, with lower values of EVLW in patients undergoing CPB with colloid primes (106,107). However, most of these studies were unable to measure differences in pulmonary edema, associated with resuscitation with either colloids or crystalloids in cardiac surgery patients (20,85,89,90).

There is evidence in the literature that some fluids influence pulmonary injury and edema, independently from the COP, by virtue of 'plugging the leaks' (108,109). Another possible mechanism includes anti-oxidant effects of both albumin and starches (110-112) and inhibition of the activation of leukocytes and the endothelium, thereby inhibiting an increase in microvascular permeability (113-116).

In conclusion, the best resuscitation fluid is unknown. There is no clear evidence from the literature that colloids are more effective than crystalloids in plasma volume expansion or in improving myocardial function, provided that enough volume is given. Furthermore, evidence is lacking that colloids are more favorable in inhibiting the genesis of pulmonary edema and improving pulmonary gas exchange. In clinical practice, the availability, costs and expertise generally determine the choice of the type of fluid given (80).

OBJECTIVES AND OUTLINES

In this part of the study, we aimed at clarifying the hemodynamic efficacy of different resuscitation fluids relative to the pulmonary side effects in critically ill patients at risk for ALI and ARDS. We included patients after cardiac or major vascular surgery with hypotension, defined as systolic blood pressure below 110 mm Hg, and hypovolemia, defined as reduced filling pressures (PCWP ≤ 10 mm Hg or CVP ≤ 8 mm Hg). We compared filling pressure-guided infusion of the colloids gelatin 4%, hydroxyethyl starch 6% and albumin 5% with normal saline 0.9%, having roughly the same colloid osmotic pressure.

In **chapter 5**, we studied the short-term hemodynamic effects of colloids compared to saline. We hypothesized that colloids are more effective in elevating intravascular volume by maintaining the COP, thereby increasing the preload of the heart and consequently cardiac output, as compared to crystalloids, which may rapidly disappear in the interstitium. We further hypothesized that exogenous colloids perform similarly to albumin in this respect. We evaluated changes in cardiac index together with plasma COP, plasma volume and cardiac performance, using a

standard pressure-guided fluid challenge protocol over 90 minutes (117). The function and loading of the heart were evaluated by calculating the left ventricular stroke work index (LVSWI) from stroke volume and mean arterial blood pressure; we measured the global end-diastolic volume of the heart (GEDV) together with the CVP. These measurements enabled us to calculate the myocardial compliance and contractility.

In **chapter 6**, we examined the effects of colloids and crystalloids on pulmonary function by simultaneously measuring gas exchange, radiological abnormalities, the COP, EVLW, the lung injury score (10) and microvascular permeability. We hypothesized that in patients at risk for an increase in microvascular permeability, colloids are superior to saline in preventing pulmonary complications, resulting in less protein extravasation, less deterioration of the chest radiograph and ventilatory variables. We also hypothesized that albumin 5% and hydroxyethyl starch lower permeability-edema, independent of the COP, either by 'plugging the leaks' or possible anti-inflammatory effects.

REFERENCES

1. Byrne K, Tatum JL, Henry DA, Hirsch JI, Crossland M, Barnes T, Thompson JA, Young J, Sugerman HJ. Increased morbidity with increased pulmonary albumin flux in sepsis-related adult respiratory distress syndrome. Crit Care Med 1992; 20: 28-34
2. Martin GS, Eaton S, Mealer M, Moss M. Extravascular lung water in patients with severe sepsis: a prospective cohort study. Crit Care 2005; 9: R74-R82
3. Sturm JA, Wisner DH, Oestern H-J, Kant CJ, Tscherne H, Creutzig H. Increased lung capillary permeability after trauma: A prospective clinical study. J Trauma 1986; 26: 409-418
4. Pallister I, Gosling P, Alpar K, Bradley S. Prediction of posttraumatic adult respiratory syndrome by albumin excretion rate eight hours after admission. J Trauma 1997; 42: 1056-1061
5. Macnaughton PD, Braude S, Hunter DN, Denison DM, Evans TW. Changes in lung function and pulmonary capillary permeability after cardiopulmonary bypass. Crit Care Med 1992; 20: 1289-1294
6. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 1995; 82: 1026-1060
7. Tenling A, Hachenberg T, Tydén H, Wegenius G, Hedenstierna G. Atelectasis and gas exchange after cardiac surgery. Anesthesiology 1998; 89: 173-178

8. Adembri C, Kastamoniti E, Bertolozzi I, Vanni S, Dorigo W, Coppo M, Pratesi C, De Gaudio AR, Gensini GF, Modesti PA. Pulmonary injury follows systemic inflammatory reaction in infrarenal aortic surgery. Crit Care Med 2004; 32: 1170-1177
9. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818-824
10. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the Adult Respiratory Distress Syndrome. Am Rev Respir Dis 1988; 138: 720-723
11. Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol. 2005 33: 319-327
12. Raijmakers PGHM, Groeneveld ABJ, Schneider AJ, Teule GJJ, van Lingen A, Eijsman L, Thijs LG. Transvascular transport of ^{67}Ga in the lungs after cardiopulmonary bypass surgery. Chest 1993; 104: 1825-1832
13. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, Schneider AJ, Teule GJJ, Hack CE, Thijs LG. Transient increase in interleukin-8 and pulmonary microvascular permeability following aortic surgery. Am J Respir Crit Care Med 1995; 151: 698-705
14. Raijmakers PGHM, Groeneveld ABJ, Teule GJJ, Thijs LG. Diagnostic value of the Gallium-67 pulmonary leak index in pulmonary edema. J Nucl Med 1996; 37: 1316-1322
15. Groeneveld ABJ, Raijmakers PGHM, Teule GJJ, Thijs LG. The ^{67}Gallium pulmonary leak index in assessing the severity and course of the adult respiratory distress syndrome. Crit Care Med 1996; 24: 1467-1472
16. Groeneveld ABJ, Raijmakers PGHM. The ^{67}gallium-transferrin pulmonary leak index in pneumonia and associated adult respiratory distress syndrome. Clinical Science 1997; 93: 463-470
17. Groeneveld ABJ. Radionuclide assessment of pulmonary microvascular permeability. Eur J Nucl Med 1997; 24: 449-461
18. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, Teule GJJ, Hack CE. Acute lung injury after aortic surgery: the relation between lung and leg microvascular permeability to ^{111}Indium-transferrin and circulating mediators. Thorax 1997; 52: 866-871
19. Groeneveld ABJ, Raijmakers PGHM. The ^{67}gallium-transferrin pulmonary leak index in patients at risk for the acute respiratory distress syndrome. Crit Care Med 1998; 26: 685-691
20. Byrick RJ, Kay JC, Noble WH. Extravascular lung water accumulation in patients following coronary artery surgery. Canad Anaesth Soc J 1977; 24: 332-345
21. Harris TR, Bernard GR, Brigham KL, et al. Lung microvascular transport properties measured by multiple indicator dilution methods in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1990; 141: 272-280

22. Hachenberg T, Tenling A, Rothen H-U, Nyström S-O, Tydén H, Hedenstierna G. Thoracic intravascular and extravascular fluid volumes in cardiac surgical patients. Anesthesiology 1993; 79: 976-984
23. Davey-Quinn A, Gedney JA, Whiteley SM, Bellamy MC. Extravascular lung water and acute respiratory distress syndrome-oxygenation and outcome. Anaesth Intensive Care 1999; 27: 357-362
24. Boussat S, Jacques T, Levy B, Laurent E, Gache A, Capellier G, Neidhart A. Intravascular volume monitoring and extravascular lung water in septic patients with pulmonary edema. Intensive Care Med 2002; 28: 712-718
25. Schuster DP, Haller J. A quantative correlation of extravascular lung water accumulation with vascular permeability and hydrostatic pressure measurements: a positron emission tomography study. J Crit Care 1990; 5: 161-168
26. Kaplan JD, Calandrino FS, Schuster DP. A positron emission tomographic comparison of pulmonary vascular permeability during the adult respiratory distress syndrome and pneumonia. Am Rev Respir Dis 1991; 143: 150-154
27. Sandiford P, Province MA, Schuster DP. Distribution of regional density and vascular permeability in the adult respiratory distress syndrome. Am J Respir Crit Care Med 1995; 151: 737-742
28. Schuster DP, Stark T, Stephenson J, Royal H. Detecting lung injury in patients with pulmonary edema. Intensive Care Med 2002; 28: 1246-1253
29. Magnusson L, Zemgulis V, Wicky S, Tydén H, Thelin S, Hedenstierna G. Atelectasis is a major cause of hypoxemia and shunt after cardiopulmonary bypass. Anesthesiology 1997; 87: 1153-1163
30. Desai SR. Acute respiratory distress syndrome: imaging of the injured lung. Clin Radiology 2002; 57: 8-17
31. Magnusson L, Spahn DR. New concepts of atelectasis during general anaesthesia. Br J Anaesthesia 2003; 91: 61-72
32. Babik B, Asztalos T, Peták F, Deák ZI, Hantos Z. Changes in respiratory mechanics during cardiac surgery. Anesth Analg 2003; 96: 1280-1287
33. Pelosi P, D'Onofrio D, Chiumello D, Paolo S, Chiara G, Capelozzi VL, Barbas CSV, Chiandara M, Gattinoni L. Pulmonary and extrapulmonary acute respiratory distress syndromes are different. Eur Respir J 2003; 22 (Suppl 42): 48S-56S
34. Dyhr T, Nygard E, Laursen N, Larsson A. Both lung recruitment maneuver and PEEP are needed to increase oxygenation and lung volume after cardiac surgery. Acta Anaesthesiol Scand 2004; 48: 187-197
35. Baudendistel L, Shields JB, Kaminski DL. Comparison of double indicator thermodilution measurement of extravascular lung water (EVLW) with radiographic estimation of lung water in trauma patients. J Trauma 1982; 22: 983-988

36. Sivak ED, Richmond BJ, O'Donavan PB, Borkowski GP. Value of extravascular lung water measurement vs portable chest x-ray in the management of pulmonary edema. Crit Care Med 1983; 11: 498-501
37. Bongard FS, Matthay M, Mackersie RC, Lewis FR. Morphologic and physiologic correlates of increased extravascular lung water. Surgery 1984; 96: 395-403
38. Halperin BD, Feeley TW, Mihm FG, Chiles C, Guthaner DF, Blank NE. Evaluation of the portable chest roentgenogram for quantifying extravascular lung water in critically ill adults. Chest 1985; 88: 649-652
39. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin R, Mascheroni M, Torresin A. Relationships between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. Anesthesiology 1988; 69: 824-832
40. Drummond GB. Computed tomography and pulmonary measurements. Br J Anaesth 1998; 80: 665-671
41. Sivak ED, Starr NJ, Graves JW, Cosgrove DM, Borsh J, Estafanous GE. Extravascular lung water values in patients undergoing coronary artery bypass surgery. Crit Care Med 1982; 10: 593-596
42. Brigham KL, Kariman K, Harris TR, Snapper JR, Bernard GR. Correlation of oxygenation with vascular permeability-surface area but not with lung water in humans with acute respiratory failure and pulmonary edema. J Clin Invest 1983; 73: 339-349
43. Sibbald WJ, Warshawski FJ, Short AK, Harris J, Lefcoe MS, Holliday RL. Clinical studies of measuring extravascular lung water by the thermal dye technique in critically ill patients. Chest 1983; 83: 725-731
44. Sibbald WJ, Short AK, Warshawski FJ, Cunningham DG, Cheung H. Thermal dye measurements of extravascular lung water in critically ill patients. Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. Chest 1985; 87: 585-592
45. Gödje O, Seebauer T, Peyerl M, Pfeiffer UJ, Reuchart B. Hemodynamic monitoring by double-indicator dilution technique in patients after orthotopic heart transplantation. Chest 2000; 118: 775-781
46. Carlile PV, Gray BA. Type of lung injury influences the thermal-dye estimation of extravascular lung water. J Appl Physiol 1984; 57: 680-685
47. Schreiber T, Hüter L, Schwarzkopf K, Schubert H, Preussler N, Bloos F, Gaser E, Karzai W. Lung perfusion affects preload assessment and lung water calculation with the transpulmonary double indicator method. Intensive Care Med 2001; 27: 1814-1818
48. Rossie P, Oldner A, Wanecek M, et al. Comparison of gravimetric and a double-indicator dilution technique for assessment of extra-vascular lung water in endotoxaemia. Intensive Care Med 2003; 29: 460-466

49. Roch A, Michelet P, Lambert D, Delliaux S, Saby C, Perrin G, Ghez O, Bregeon F, Thomas P, Carpentier J-P, Papazian L, Auffrey J-P. Accuracy of the double indicator method for measurement of extravascular lung water depends on the type of acute lung injury. Crit Care Med 2004; 32: 811-817
50. Ng CSH, Wan S, Yim APC, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest 2002; 121: 1269-1277
51. Asimakopoulos G, Smith PLC, Ratnatunga CP, Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999; 68: 1107-1115
52. Milot J, Perron J, Lacasse Y, Létourneau L, Cartier PC, Maltais F. Incidence and predictors of ARDS after cardiac surgery. Chest 2001; 119: 884-888
53. Tassani P, Schad H, Winkler C, Bernhard A, Ettner U, Braun SL, Eising GP, Kochs E, Lange R, Richter JA. Capillary leak syndrome after cardiopulmonary bypass in elective, uncomplicated coronary bypass grafting operations: Does it exist? J Thoracic Cardiovasc Surg 2002; 123: 735-741
54. Von Spiegel T, Giannaris S, Wietasch GJK, Schroeder S, Buhre W, Schorn B, Hoeft A. Effects of dexamethasone on intravascular and extravascular fluid balance in patients undergoing coronary bypass surgery with cardiopulmonary bypass. Anesthesiology 2002; 96: 827-834
55. Louagie Y, Gonzalez E, Jamart J, Bulliard G, Schoevaerdts J-C. Postcardiopulmonary lung edema. A preventable complication? Chest 1993; 103: 86-95
56. Gilbert TB, Barnas GM, Sequeira AJ. Impact of pleurotomy, continuous positive airway pressure, and fluid balance during cardiopulmonary bypass on lung mechanics and oxygenation. J Cardiothorac Vasc Anesth 1996; 10: 844-849
57. Polese G, Lubli P, Mazzucco A, Luzzani A, Rossi A. Effects of open heart surgery on respiratory mechanics. Intensive Care Med 1999; 25: 1092-1099
58. Ranieri VM, Vitale N, Grasso S, Puntillo F, Mascia L, Paparella D, Tunzi P, Giuliani R, De Luca Tupputi L, Fiore T. Time-course of impairment of respiratory mechanics after cardiac surgery and cardiopulmonary bypass. Crit Care Med 1999; 27: 1454-1460
59. Jayr C, Matthay MA, Goldstone J, Gold WM, Wiener-Kronish JP. Preoperative and intraoperative factors associated with prolonged mechanical ventilation. A study in patients following major abdominal vascular surgery. Chest 1993; 103: 1231-1236
60. Volta CA, Ferri E, Marangoni E, Ragazzi R, Verri M, Alvisi V, Zardi S, Bertacchini S, Gritti G, Alvisi R. Respiratory function after aortic aneurysm repair: a comparison between retroperitoneal and transperitoneal approaches. Intensive Care Med 2003; 29: 1258-1264
61. Pararajasingam R, Nicholson ML, Bell PRF, Sayers RD. Non-cardiogenic pulmonary oedema in vascular surgery. Eur J Vasc Endovasc Surg 1999; 17: 93-105
62. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Am J Respir Crit Care Med 1998; 158: 3-11

63. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Intensive Care Med 2000; 26: 1215-27
64. Boldt J. Volume therapy in cardiac surgery: does the kind of fluid matter? J Cardiothor Vasc Anesth 1999; 13: 752-763.
65. Boldt J. Volume replacement in the surgical patient - does the type of solution make a difference? Br J Anaesth 2000; 84: 783-793
66. Gan TJ, Sopitt A, Maroof M, El-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PSA. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97: 820-826
67. Treib J, Baron J-F, Grauer MT, Strauss RG. An international view of hydroxyethyl starches. Intensive Care Med 1999; 25: 258-268
68. Nolan J. Fluid resuscitation for the trauma patient. Resuscitation 2001; 48: 57-69
69. Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. Anesth Analg 2005; 100: 1093-1106
70. Velanovich V. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. Surg 1989; 105: 65-71
71. Bisonni RS, Holtgrave DR, Lawler F, Marley DS. Colloids versus crystalloids in fluid resuscitation: an analysis of randomized controlled trials. J Fam Practice 1991; 32: 387-390
72. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systemic review of randomized trials. BMJ 1998; 316: 961-964
73. Choi PT-L, Yip G, Quinonez LG, Cook DJ. Crystalloids versus Colloids in fluid resuscitation: A systemic review. Crit Care Med 1999; 27: 200-210
74. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2004; Oct 18: CD000567
75. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systemic review of randomized controlled trials. BMJ 1998; 317: 235-239
76. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. Ann Intern Med 2001; 135: 149-164
77. Imm A, Carlson RW. Fluid resuscitation in circulatory shock. Crit Care Clin 1993; 9: 313-333
78. Messmer KFW. The use of plasma substitutes with special attention to their side effects. World J Surg 1987; 11: 69-74
79. Nearman HS, Herman ML. Toxic effects of colloids in the intensive care unit. Crit Care Clin 1991; 7: 713-723
80. Boldt J. Lenz M, Kumle B, Papsdorf M. Volume replacement strategies on intensive care units: results from a postal survey. Int Care Med 1998; 24: 147-151

81. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. Intensive Care Med 1992; 18: 142-147
82. Hoeft A, Schorn B, Weyland A, Scholz M, Buhre W, Stepanek E, Allen SJ, Sonntag H. Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. Anesth 1994; 81: 76-86
83. Wiesenack C, Prasser C, Keyl C, Rödig G. Assessment of intrathoracic blood volume as an indicator of cardiac preload: single transpulmonary thermodilution technique versus assessment of pressure preload parameters derived from a pulmonary artery catheter. J Cardiothorac Vasc Anesth 2001; 15: 584-588
84. Rackow EC, Falk JL, Fein IA, Siegel JS, Packman MI, Haupt MT, Kaufman BS, Putnam D. Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 1983; 11: 839-850
85. Karanko MS, Klossner JA, Laaksonen VO. Restoration of volume by crystalloid versus colloid after coronary bypass: Hemodynamics, lung water, oxygenation, and outcome. Crit Care Med 1987; 15: 559-566
86. Morisaki K, Bloos F, Keys J, Martin C, Neal A, Sibbald WJ. Compared with crystalloid, colloid therapy slows progression extrapulmonary tissue injury in septic sheep. J Appl Physiol 1994; 77: 1507-1518
87. Boutros AR, Ruess R, Olson L, Hoyt JL, Baker WH. Comparison of hemodynamic, pulmonary, and renal effects of use of three types of fluid after major surgical procedures on the abdominal aorta. Crit Care Med 1979; 7: 9-13
88. Zetterström H. Albumin treatment following major surgery. II. Effects on postoperative lung function and circulatory adaptation. Acta Anaesth Scand 1981; 25: 133-141
89. Gallagher JD, Moore RA, Kerns D, Jose AB, Botros SB, Flicker S, Naidech H, Clark DL. Effects of colloid or crystalloid administration on pulmonary extravascular lung water in the postoperative period after coronary bypass grafting. Anesth Analg 1985; 64: 753-758
90. Wahba A, Sendtner E, Strotzer M, Wild K, Birnbaum DE. Fluid therapy with Ringer's solution versus Haemacel following coronary artery bypass surgery. Acta Anaesthesiol Scand 1996; 40: 1227-1233
91. The SAFE Study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350: 2247-2256
92. Hankeln K, Rädel C, Beez M, Laniewski P, Bohmert F. Comparison of hydroxyethyl starch and lactated Ringer's solution on hemodynamics and oxygen transport of critically ill patients in prospective crossover studies. Crit Care Med 1989; 17: 133-135
93. Ley SJ, Miller K, Skov P, Preisig P. Crystalloid versus colloid fluid therapy after cardiac surgery. Heart Lung 1990; 19: 31-40

94. London MJ, Ho JS, Triedman JK, Verrier ED, Levin J, Merrick SH, Hanley FL, Browner WS, Mangano DT. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg 1989; 97: 785-797
95. Mastroianni L, Low HBC, Rollman J, Wagle M, Bleske B, Chow MSS. A comparison of 10% pentastarch and 5% albumin in patients undergoing open-heart surgery. J Clin Pharmacol 1994; 34: 34-40
96. Boldt J, Heesen M, Müller M, Pabsdorf M, Hempelmann G. The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. Anest Analg 1996; 83: 254-261
97. Zikria BA, Subbarao C, Oz MC, Popilkis SJ, Sachdev R, Chauban P, Freeman HP, King TC. Hydroxyethyl starch macromolecules reduce myocardial reperfusion injury. Arch Surg 1990; 125: 930-934
98. Dahn MS, Lucas CE, Ledgerwood AM, Higgins RF. Negative inotropic effect of albumin resuscitation for shock. Surg 1979; 86: 235-241
99. Magder S, Lagonidis D. Effectiveness of albumin versus normal saline as a test of volume responsiveness in post-cardiac surgery patients. J Crit Care 1999; 14: 164-171
100. Laks H, Standeven J, Blair O, Hahn J, Jellinek M, Willman VL. The effects of cardiopulmonary bypass with crystalloid and colloid on myocardial water. J Thoracic Cardiovasc Surg 1977; 73: 129-138
101. Foglia RP, Partington MT, Buckberg GD, Leaf J. Iatrogenic myocardial edema with crystalloid primes. Effects on left ventricular compliance, performance, and perfusion. Curr Stud Hematol Blood Transf 1986; 53: 53-63
102. Hsu DT, Weng Z-C, Nicolosi AC, Detwiler PW, Sciacca R, Spotnitz HM. Quantitative effects of myocardial edema on the left ventricular pressure-volume relation. J Thoracic Cardiovasc Surg 1993; 106: 651-657
103. Mehlhorn U, Allen SJ, Davis KL, Geissler HJ, Warters RD, Rainer de Vivie E. Increasing the colloid osmotic pressure of cardiopulmonary bypass prime and normothermic blood cardioplegia minimizes myocardial oedema and prevents cardiac dysfunction. Cardiovasc Surg 1998; 6: 274-281
104. Metildi LA, Shackford SR, Virgilio RW. Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency, Surg Gynecol Obstet 1984; 158: 207-212
105. Tølløfsrud S, Svennevig JL, Breivik H, Kongsgaard U, Øzer M, Hysing E, Mohr B, Seem E, Geiran O, Abdelnour M, Frøysaker T, Noddeland H. Fluid balance and pulmonary functions during and after coronary artery bypass surgery: Ringer's acetate compared with dextran, polygeline, or albumin. Acta Anaesthesiol Scand 1995; 39: 671-677

106. Hoeft A, Korb H, Mehlhorn U, Stephan H, Sonntag H. Priming of cardiopulmonary bypass with human albumin or ringer lactate: effect on colloid osmotic pressure and extravascular lung water. Br J Anaesth 1991; 66: 73-80
107. Eising GP, Niemeyer M, Günther Th, Tassani P, Pfauder M, Schad H, Lange R. Does a hyperoncotic cardiopulmonary bypass prime affect extravascular lung water and cardiopulmonary function in patients undergoing coronary bypass surgery? Eur J Cardiothoracic Surg 2001; 20: 282-289
108. Zikria BA, King TC, Stanford J, Freeman HP. A biophysiological approach to capillary permeability. Surg 1989; 105: 625-631
109. Wisselink W, Patetsios P, Panetta TF, Ramirez JA, Rodino W, Kirwin JD, Zikria BA. Medium molecular weight pentastarch reduces reperfusion injury by decreasing capillary leak in an animal model of spinal cord ischemia. J Vasc Surg 1998; 27: 109-116
110. Nielsen VG, Tan S, Brix AE, Baird MS, Parks DA. Hextend (hetastarch solution) decreases multiple organ injury and xanthine oxidase release after hepatoenteric ischemia-reperfusion in rabbits. Crit Care Med 1997; 25 :1565-1574
111. Axon RN, Baird MS, Lang JD, Brix AE, Nielsen VG. Pentalyte decreases lung injury after aortic occlusion-reperfusion. Am J Respir Crit Care Med 1998; 157: 1982-1990
112. Chiang C-H, Wu C-P, Perng W-C , Yan H-C, Yu C-P. Dexamethasone and pentastarch produce additive attenuation of ischemia/reperfusion lung injury. Clin Science 2000; 99: 413-419
113. Collis RE, Collins PW, Gutteridge CN, Kaul A, Newland AC, Williams DM, Webb AR. The effect of hydroxyethyl starch and other plasma volume substitutes on endothelial cell activation; an in vitro study. Intensive Care Med 1994; 20: 37-41
114. Oz MC, FitzPatrick MF, Zikria BA, Pinsky DJ, Duran WN. Attenuation of Microvascular Permeability Dysfunction in Postischemic Striated Muscle by Hydroxyethyl Starch. Microvasc Res 1995; 50: 71-79
115. Hofbauer R, Moser D, Hornykewycz S, Frass M, Kapiotis S. Hydroxyethyl starch reduces the chemotaxis of white cells through endothelial cell monolayers. Transfusion 1999; 39: 289-294
116. Boldt J, Müller M, Heesen M, Neumann K, Hempelmann GG. Influence of different volume therapies and pentoxifylline infusion on circulating soluble adhesion molecules in critically ill patients. Crit Care Med 1996; 24: 385-391
117. Weil MH, Henning RJ. New concepts in the diagnosis and fluid treatment of circulatory shock. Thirteenth Annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture. Anesth Analg 1979; 58: 124-132

CHAPTER 2

Pulmonary abnormalities after cardiac surgery are better explained by atelectasis rather than increased permeability edema

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ABSTRACT

Background. Cardiac surgery can be complicated by pulmonary abnormalities, but it is unclear how various manifestations interrelate.

Methods. A prospective study in the intensive care unit was done on 26 mechanically ventilated patients without cardiac failure, within three hours after elective cardiac surgery involving cardiopulmonary bypass. Edema (extravascular lung water, EVLW) was measured by the thermal-dye technique, permeability by a dual radionuclide technique yielding a pulmonary leak index (PLI), and radiographic, mechanical and gas exchange features were used to calculate the lung injury score (LIS), ranging between 0 and 4. Evidence for left lower lobe atelectasis was obtained from plain radiographs. The plasma colloid osmotic pressure (COP) was measured by an oncometer.

Results. The EVLW (normal <7 mL/kg) was elevated in 36% of patients and the PLI (normal <14.1 x 10^{-3}/min) in 44%, but the variables did not directly interrelate. Patients with a supranormal EVLW had a lower COP than patients with normal EVLW. The duration of mechanical ventilation was prolonged in patients (20%) with EVLW >10 mL/kg. There was no difference in EVLW and PLI in patients with a LIS <1 and >1 (31% of patients). In patients with radiographic evidence for atelectasis (46%), the positive end-expiratory pressure and inspiratory O_2 fraction to maintain oxygenation were higher than in those without.

Conclusions. After cardiac surgery, mild pulmonary edema is relatively common, even in the absence of high filling pressures, and mainly attributable to a low COP, irrespective of increased permeability in about half of patients. It may prolong mechanical ventilation at EVLW >10 mL/kg. However, pulmonary radiographic and ventilator abnormalities may result, at least in part, from atelectasis rather than from increased permeability edema.

INTRODUCTION

Cardiac surgery carries a variety of pulmonary complications, some of them contributing to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (1,2). They may consist of increased pulmonary capillary protein permeability (3-5), increased extravascular lung water (EVLW) or edema (6-20) and atelectasis (15,21-24), which, either alone or together, may contribute to radiographic, mechanical and gas exchange abnormalities, hypoxemia, temporary ventilator-dependency and ultimate morbidity and mortality, at least in some patients (25,26). Although risk factors for some of these changes have been identified (2,6,12,14), the prevalence of pulmonary complications widely varies between studies, when looking at the different manifestations. For instance, the increase in EVLW after surgery has been claimed to be minimal in some reports but substantial in others (6,7,10-13,19,20,23,26). As measured by non-invasive radionuclide techniques, pulmonary capillary protein permeability may increase in some patients, probably as a result of ischemia, reperfusion and a proinflammatory response (25,27), but not in others (3-5,28). Moreover, it is unclear if and how the ALI-ARDS criteria, i.e. radiographic, mechanical and oxygenation changes on the one hand and permeability and edema on the other, overlap or interrelate (3,4,6,7,13,15,24,25,26,29). For instance, (transient) lung edema after cardiac surgery can been caused by increased permeability (3-5), a low colloid osmotic pressure (6,8,12,18), or a high hydrostatic filtration pressure in the lungs (6,11,14), and may or may not affect the chest radiograph, lung mechanics and oxygenation (6,7,13,23,26). Indeed, a fall in oxygenation and lung compliance might be caused by atelectasis rather than by increased permeability and edema, as suggested by computer tomography (CT) scanning, even though alveolar collapse is hard to measure (3,4,7,15,18,21-24,30). Indeed, CT may only poorly differentiate between fluid, e.g. edema, and atelectasis (31). Differentiating is important since the latter more likely responds to recruitment maneuvers than the former (32). Taken together, the interrelationship between the various manifestations of pulmonary complications after cardiac surgery is unclear, and the role of increased permeability and edema in radiographic and ventilatory abnormalities can be doubted.

To evaluate the occurrence and causes of pulmonary edema and to assess its contribution, versus atelectasis, in lung radiographic, gas exchange and mechanical abnormalities, we studied 26 mechanically ventilated patients within three hours after cardiac surgery involving cardiopulmonary bypass without signs of cardiac failure, in whom EVLW, capillary permeability, gas exchange, radiographic and ventilatory parameters were measured simultaneously and independently in the intensive care unit (ICU).

PATIENTS AND METHODS

This is a prospective study, approved by the Ethical Committee of the Vrije Universiteit Medical Centre, involving 26 consecutive patients after elective cardiac surgery involving cardiopulmonary bypass. In this university hospital, about 750 open heart procedures are performed per year. Written informed consent was obtained pre-operatively in eligible patients (n=52). The inclusion criteria were the presence of a pulmonary artery (n=24) or central venous catheter (n=2), postoperatively. Exclusion criteria were an age above 79 years and pregnancy (prior to surgery), a life expectancy less than 24 hours and signs of cardiac failure, defined by a cardiac index (CI) below 2.0 L/min/m^2 and a central venous pressure (CVP) above 13 or pulmonary capillary wedge pressure (PCWP) above 15 mm Hg, after surgery at arrival in the ICU (14). On the day of the surgery, anesthesia was induced with sufentanil, pancuronium and midazolam, and maintained with a continuous infusion of propofol. At induction, 50-100 mg of dexamethasone was administered. Radial artery, central venous and pulmonary artery catheters were inserted for hemodynamic measurements and blood sampling. After tracheal intubation, the lungs were volume-controlled ventilated with a tidal volume (V_t) of 8-10 mL/kg resulting in an end-tidal CO_2 concentration between 4 and 5%, using an O_2-air mixture with an inspiratory O_2 fraction (F_iO_2) of 40% and a positive end-expiratory pressure (PEEP) of 5 cm H_2O (I:E 1:2). The patients underwent cardiopulmonary bypass (CPB) during which the lungs were not ventilated. The extracorporeal circulation system was primed with 300 mL of Ringer's lactate, 1000 mL of gelatin 4%, 100 mL of 20% mannitol, 50 mL of 8.4% sodium bicarbonate, 200 mL of aprotinine and 5000 IU of heparin (33). After systemic heparinization (300 IU/kg), CPB

(Stockert-Sorin S3, Sorin Biomedica, Mirandola, Modena, Italy) was started, provided that the activated clotting time was more than 480 sec. Non-pulsatile flow rate was maintained at 2-3 L/min/m^2, depending on the acid-base balance, pre-operative cardiac output and lactate concentrations. Patients were cooled to 32 °C nasopharyngeal temperature. Mean arterial pressure (MAP) was maintained at 50-80 mm Hg during CPB and if the MAP declined to less than 50 mm Hg, the blood flow rate was increased, or vaso-active drugs were given. After aortic cross-clamping, all patients received crystalloid cardioplegia for myocardial protection (in total, ± 2000 mL, potassium 16 mmol/L, 4 °C). Patients were weaned from CPB using inotropic support, if necessary. After termination of CPB, heparin was neutralized using an equivalent dose of protamine sulphate 3 mg/kg. Autologous blood and residual volume from the extracorporeal circuit were infused as first-choice fluid administration. Guided by low systemic and filling pressures, NaCl 0.9%, gelatin or starches were infused additionally. If the hemoglobin concentration was less than 6 mmol/L, packed red blood cells concentrates were infused. At the end of surgery, a 4F introducing sheath (Arrow, Reading, USA) was inserted into the femoral artery, for use in the study protocol, in each patient. No ventilatory recruitment maneuvers were attempted.

Table 1. Patient characteristics

Age, year	61 (38-74)
Sex, M/F	19 (73)/ 7 (27)
Prior myocardial infarction	12 (46)
Smoking history/COPD	5 (19)
CPB time, min	112 (40-198)
Type of surgery	
CABG	17 (65)
AVR with or without CABG	7 (27)
ASD	2 (8)
LIMA	5 (19)
APACHE II	9 (2-14)
On vasoactive drugs	
Dopamine	18 (69)
Nitroglycerin	22 (85)

Median and ranges or number of patients (%), where appropriate. Abbreviations: COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; CABG = coronary artery bypass grafting; AVR = aortic valve replacement; ASD = atrial septal defect repair; LIMA = left internal mammary artery; APACHE = acute physiology and chronic health evaluation.

EVLW was measured in 25 patients with help of the thermal-dye technique, after exclusion of one patient with catheter malposition (17). A 3F fiberoptic thermodilution

catheter was inserted in the femoral artery sheath. Fifteen mL of ice cold indocyanine green (ICG), 1 mg/mL D5W, was injected in a central vein and the thermal-dye dilution curve obtained at the femoral artery (COLD Z-021, Pulsion Medical Systems, Munich, Germany). This allowed calculation of the transpulmonary cardiac output, the intrathoracic blood volume (ITBV), the pulmonary blood volume (PBV) and the extravascular thermal volume in the lungs as a measure of EVLW (normal <7 mL/kg) (13,17). EVLW is typically two to three-fold elevated in case of overt (radiographic) pulmonary edema (17,29). The normal ratio of EVLW/ITBV (mL/mL) is 0.2 to 0.3 and the normal EVLW/PBV ratio is about 1, and the indices have been proposed to reflect permeability (19,29,34). Measurements were done in duplicate and averaged. The cardiac output was indexed to body surface area (cardiac index, CI).

PLI was measured in 25 patients (4,28). Logistics precluded a measurement in one patient. In brief, autologous red blood cells were labeled with ^{99m}Tc (11 MBq, physical half-life 6h; Mallinckrodt Diagnostica, Petten, The Netherlands). Transferrin was labeled in vivo, following i.v. injection of ^{67}Ga-citrate, 4.5 MBq (physical half-life 78 h; Mallinckrodt Diagnostica, Petten, The Netherlands). Patients were in the supine position and two scintillation detection probes (Eurorad C.T.T., Strasburg, France) were positioned over the right and left lung apices. Starting at the time of injection of ^{67}Ga, radioactivity was detected every minute, during 30 minutes. The count rates were corrected for background radioactivity, physical half-life and spill-over and expressed as counts per minute (CPM) per lung field. Until 30 minutes after ^{67}Ga injection, blood samples (2 mL aliquots) were taken. Each blood sample was weighed and radioactivity was determined with a single well well-counter, corrected for background, spillover and decay (LKB Wallac 1480 WIZARD, Perkin Elmer, Life Science, Zaventem, Belgium). Results were expressed as CPM/g. For each blood sample, a time-matched CPM over each lung was taken. A radioactivity ratio was calculated, ($^{67}Ga_{lung}$/$^{99m}Tc_{lung}$)/($^{67}Ga_{blood}$/$^{99m}Tc_{blood}$), and plotted against time. The PLI was calculated, using linear regression analysis, from the slope of increase of the radioactivity ratio divided by the intercept. The PLI represents the transport rate of ^{67}Ga from the intravascular to the extravascular space of the lungs and is therefore a measure of pulmonary vascular permeability (4,28). The values for both lung fields were averaged. The upper limit of normal for the PLI is 14.1 x 10^{-3}/min and the measurement error is about 10% (4,28).

The PLI is typically elevated more than three- to fourfold in ARDS (4,28).

Radiography and lung injury score (LIS). The latter was calculated from the number of quadrants on the chest radiograph with opacities, the PEEP level, the arterial PO_2 (P_aO_2)/inspiratory O_2 fraction (F_iO_2) and the dynamic total respiratory compliance (35). The compliance was calculated from tidal volume/(plateau pressure-PEEP), mL/cm H_2O. The chest radiograph was scored by a consultant radiologist, blinded to the study, who evaluated the number of quadrants with alveolar opacities, ranging from 0 to 4. In addition, the presence of blurring of the left hemidiaphragm and costophrenic angle by alveolar opacification was recorded as radiographic evidence for left lower lobe atelectasis. The LIS ranges between 0 (no injury) to 4, with values above 2.5 indicative of ARDS, and between 0 and 2.5 of ALI (35).

Protocol. After surgery, the patients were admitted to the ICU. The patients were connected to the ventilator (Evita 4, Dräger, Lübeck, Germany) and volume-controlled ventilation was started with similar settings as during surgery. Demographics were recorded, including the acute physiology and chronic health evaluation (APACHE-II) score, measurements of EVLW, ^{67}Ga-transferrin PLI and hemodynamics were performed, and an anteroposterior chest radiograph was made. Hemodynamic variables were measured after calibration and zeroing to atmospheric pressure at mid-chest level (Tramscope^R, Marquette, Wisc., USA). Mean pulmonary artery pressure (MPAP), CVP and, after balloon inflation, the PCWP were taken at end-expiration, with patients in the supine position, if adequate tracings for the latter could be obtained (n=17). Arterial blood samples were obtained for determinations of partial O_2/CO_2 pressures and O_2 saturations (Rapidlab 865, Bayer Diagnostics, Tarrytown, NY, USA, at 37 °C), hemoglobin, albumin and total protein levels (Roche/Hitachi 747, Roche Diagnostics Corporation, Indianapolis, IN, USA). Mixed (n=24) or central (n=2) venous blood was taken simultaneously for measurement of partial pressures and saturations. Shunt fraction (Q_s/Q_t) was calculated according to standard formulae. The plasma colloid osmotic pressure (COP) was measured by a membrane osmometer (Osmomat 050, Gonotex, Berlin, Germany, molecular cut-off at 20 kDa, normal about 24 mm Hg). The F_iO_2, tidal volume, plateau inspiratory pressure and PEEP (cm H_2O) were taken from the ventilator. Doses of vasoactive drugs were recorded. Patients were taken care of by intensive care physicians not involved in the study and followed until extubation

and discharge/death in the ICU. The duration of mechanical ventilation was defined as the interval from admission to extubation.

Table 2. Post cardiac surgery patients with and without pulmonary edema or increased permeability

	EVLW <7 ml/kg n=16	EVLW >7 ml/kg n=9	PLI <0.0014/min n=14	PLI >0.0014/min n=11
Hemodynamics				
MAP, mm Hg	74 (52-104)	80 (66-102)	72 (52-102)	84 (63-104)[4]
CVP, mm Hg	5 (0-7)	6 (2-12)	6 (0-12)	4 (0-7)
PCWP, mm Hg	n=10	n=6	n=10	n=6
	8 (1-11)	9 (4-13)	8 (3-13)	7 (1-10)
MPAP, mm Hg	14 (8-22)	18 (12-23)	18 (9-23)	13 (8-21)
CI, L/min/m^2	3.1 (2.4-4.3)	2.6 (2.2-3.5)[3]	3.2 (2.2-4.3)	2.7 (2.3-3.8)
COP, mm Hg	19 (18-22)	18 (15-20)[1]	19 (15-21)	19 (15-22)
Pulmonary changes				
PLI, x 10^{-3}/min	n=16	n=8	n=14	n=11
	18 (8-60)	13 (6-24)[4]	11 (6-15)	24 (19-60)[7]
Supranormal PLI	8 (50)	2 (25)	na	na
EVLW, mL/kg	n=16	n=9	n=14	n=10
	5.3 (2.1-6.7)	10.3 (7.1-20.0)[7]	6.3 (3.7-20.0)	5.6 (2.1-8.3)
Supranormal EVLW	na	na	6 (43)	2 (20)
EVLW/ITBV	0.19 (0.08-0.47)	0.43 (0.26-0.63)[7]	0.29 (0.13-0.63)	0.19 (0.08-0.48)
EVLW/PBV	1.0 (0.3-2.9)	3.5 (1.2-8.7)[7]	1.5 (0.6-8.7)	0.9 (0.3-4.4)
P_aO_2, mm Hg	114 (92-174)	119 (84-189)	108 (84-185)	155 (92-184)
F_iO_2, %	41 (39-61)	40 (39-62)	43 (39-62)	40 (39-51)
P_aO_2/F_iO_2	263 (164-435)	290 (140-485)	244 (140-463)	355 (202-472)[2]
Q_s/Q_t, %	15 (10-28)	13 (6-62)	18 (9-62)	14 (10-28)
PEEP, cm H_2O	7 (5-16)	8 (5-15)	7 (5-16)	6 (5-8)[5]
P_{plat}, cm H_2O	16 (14-33)	18 (13-28)	17 (13-33)	18 (14-22)
V_t, mL	547 (395-1110)	550 (500-670)	535 (459-1110)	550 (395-670)
Compliance, mL/cm H_2O	51 (38-80)	50 (39-83)	59 (38-83)	48 (38-69)[5]
Radiographic quadrants	0 (0-2)	0 (0-3)	0 (0-3)	0 (0-2)
Atelectasis	10 (63)	2 (22)[6]	9 (64)	3 (27)
LIS	1.0 (0.2-1.7)	0.7 (0.5-2.7)	1.0 (0.5-2.7)	0.7 (0.2-1.2)
Duration mechanical ventilation, h				
	11 (5-19)	11 (5-494)	12 (5-494)	10 (5-15)

Median (ranges or %, where appropriate); Abbreviations: MAP = mean arterial pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; MPAP = mean pulmonary arterial pressure; CI = cardiac index; COP = colloid osmotic pressure; PLI = pulmonary leak index; EVLW = extravascular lung water; ITBV = intrathoracic blood volume; PBV = pulmonary blood volume; a = arterial; F_iO_2 = inspiratory O_2 fraction; Q_s/Q_t = shunt fraction; PEEP = positive end-expiratory pressure; P_{plat} = plateau pressure; V_t = tidal volume; LIS = lung injury score; na = not applicable. P (exact if <0.10): [1]P=0.02, [2]P=0.05, [3]P=0.06, [4]P=0.07, [5]P=0.09, [6]P=0.10, [7]P=na

Statistical analysis. We dichotomized groups with normal and elevated (>7 mL/kg) EVLW, normal and elevated (>14.1 x 10^{-3}/min) PLI and a LIS below and above 1. Data were summarized as median and range and groups were compared with help of the non-parametric Mann-Whitney U test for unpaired data. Fisher's exact test was used to compare frequencies. The Spearman correlation coefficient was used to express relations. Exact P values below 0.10 are given.

RESULTS

The postoperative course was uneventful in all but one patient, in spite of relatively low oxygenation ratios and dynamic compliances shortly after surgery. The patients (except for one) were transferred from the ICU to special postcardiac surgery wards on the day after surgery. One patient died 9 days after admission following pulmonary hemorrhage. Table 1 includes some details on patient characteristics. There were no differences in vasoactive support or in P_aCO_2 among subgroups.

Pulmonary edema (EVLW >7 mL/kg, Table 2). The EVLW was mildly elevated in 36% of patients, independently of ITBV or PBV, and COP was lower in patients with an elevated EVLW. Compared with patients with a normal EVLW, those with an elevated EVLW had a lower COP-CVP gradient, i.e. 14 (12-21) in the former and 12 (6-15) mm Hg in the latter (P=0.009). The EVLW, EVLW/ITBV and EVLW/PBV inversely correlated to the COP-CVP (minimum r_s=-0.49, P=0.016, Figure 1), while the relations to either COP or CVP alone were weaker. The COP inversely correlated to CPB time (r_s=-0.51, P=0.009). Five patients (20%) had an EVLW of 10 mL/kg or higher and their duration of mechanical ventilation was longer (P=0.042) than in patients with EVLW <10 mL/kg. EVLW did not relate to LIS nor its components.

Increased permeability (PLI >14.1 x 10^{-3}/min, Table 2). An elevated PLI was present in 44% of patients. There were no differences in study variables between patients with normal and elevated PLI, except for a higher oxygenation ratio in the latter. The PLI weakly and inversely related to the EVLW, EVLW/PBV and EVLW/ITBV (minimum r_s= -0.42, P=0.042) and to PEEP and dynamic compliance (minimum r_s=-0.40, P=0.049).

Atelectasis. Table 3 describes patients with or without radiographic evidence for left lower lobe atelectasis. The presence of atelectasis coincided with a higher PEEP and F_iO_2 necessary to maintain oxygenation than the absence of atelectasis. There was no difference in compliance between patients with or without evidence for atelectasis.

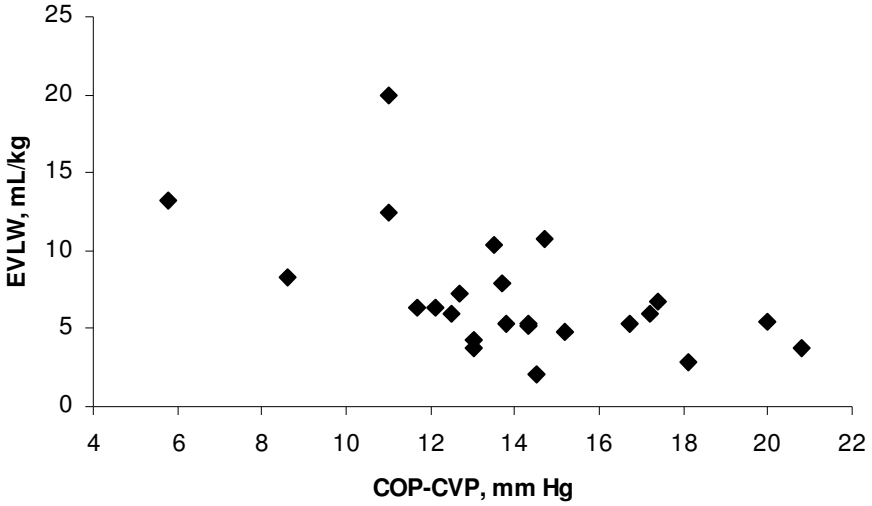

Figure 1. Inverse relation between extravascular lung water (EVLW, n <7 mL/kg) and pressure gradient between plasma colloid osmotic (COP) and central venous pressure (CVP) in 26 patients after cardiac surgery: r_s=-0.58, P=0.003

LIS (Table 3). There was one patient with a LIS >2.5 and 3 quadrants of alveolar opacities on chest radiography. This patient had a PLI of 14.0 x 10^{-3}/min, an EVLW of 13 mL/kg, a COP of 18 mm Hg, PCWP of 13 mm Hg and evidence for atelectasis. Otherwise, patients with a low (<1) or high (>1, 31%) LIS did not differ in EVLW nor in PLI, but in the clinical variables composing the LIS, which were more severely affected in the high LIS group. In addition, cardiac filling pressures (and MPAP) were higher in patients with high LIS and relatively high PEEP than in those with low values. Indeed, the MPAP, PCWP and CVP related to PEEP (minimum r_s=0.51, P=0.01). The LIS directly related to Q_s/Q_t (r_s=0.46, P=0.01), the latter tending to differ between LIS groups.

Table 3. Patients without or with lung injury or radiographic evidence for left lower lobe atelectasis

	No atelectasis n=14	With atelectasis n=12	LIS <1 n=18	LIS >1 n=8
Hemodynamics				
MAP, mm Hg	82 (63-102)	73 (52-104)	79 (58-104)	71 (52-102)
CVP, mm Hg	4 (0-7)	5 (0-12)	4 (0-6)	7 (5-12)[1]
PCWP, mm Hg	n=9	n=8	n=11	n=6
	7 (3-10)	9 (1-13)[5]	7 (1-11)	9 (7-13)
MPAP, mm Hg	14 (10-22)	17 (8-23)	14 (8-21)	18 (13-23)[3]
CI, L/min/m^2	2.8 (2.2-3.8)	3.1 (2.5-4.3)	2.7 (2.2-4.3)	3.2 (2.6-3.5)
COP, mm Hg	19.3 (14.6-20.7)	18.9 (17.8-21.7)	18.7 (14.6-21.7)	19.0 (17.8-20.8)
Pulmonary changes				
PLI, $x10^{-3}$/min	n=13	n=12	n=17	n=8
	20 (6-60)	13 (8-53)	19 (8-60)	14 (6-30)
Supranormal PLI	8 (62)	3 (25)	9 (53)	2 (25)
EVLW, mL/kg	n=13	n=12	n=17	n=8
	7.1 (2.1-20.0)	5.3 (2.9-13.2)	5.4 (2.1-20.0)	6.4 (5.2-13.2)
Supranormal EVLW	7 (54)	2 (17)[7]	6 (35)	3 (38)
EVLW/ITBV, mL/mL	0.26 (0.08-0.63)	0.27 (0.13-0.47)	0.25 (0.08-0.63)	0.28 (0.18-0.47)
EVLW/PBV, mL/mL	1.26 (0.27-8.75)	1.42 (0.59-4.03)	1.4 (0.3-8.7)	1.3 (0.8-4.0)
P_aO_2, mm Hg	125 (84-189)	121 (93-173)	143 (84-189)	106 (87-174)
F_iO_2	40 (39-62)	43 (39-61)[4]	40 (39-51)	50 (40-62)[2]
P_aO_2/F_iO_2	316 (140-485)	263 (164-422)	349 (202-485)	227 (140-435)[8]
Q_s/Q_t, %	13 (5-29)	17 (14-62)[7]	14 (5-29)	18 (12-62)[6]
PEEP, cm H_2O	5 (5-10)	7 (5-16)[3]	5 (5-9)	10 (7-16)[8]
P_{plat}, cm H_2O	17 (13-22)	18 (14-33)	17 (13-22)	17 (15-33)
V_t, mL	550 (395-670)	550 (420-1110)	560 (420-670)	510 (395-1110)
Compliance, mL/cm H_2O	50 (39-83)	51 (38-80)	50 (38-80)	53 (39-83)[8]
Radiographic quadrants	0 (0-2)	0 (0-3)	0 (0-1)	1 (0-3)[8]
Atelectasis	na	na	7 (39)	5 (63)
LIS	0.7 (0.2-1.2)	1.0 (0.5-2.7)	0.7 (0.2-1.0)	1.4 (1.2-2.7)[8]
Duration mechanical ventilation, h				
	11 (5-316)	11 (8-494)	12 (5-316)	11 (6-494)

Median (ranges or %, where appropriate); N = number of patients. Abbreviations: MAP = mean arterial pressure; CVP = central venous pressure; PCWP = pulmonary artery occlusion pressure; MPAP = mean pulmonary artery pressure; CI = cardiac index; COP = colloid osmotic pressure; PLI = pulmonary leak index; EVLW = extravascular lung water; ITBV = intrathoracic blood volume; PBV = pulmonary blood volume; a = arterial; F_iO_2 = inspiratory O_2 fraction; Q_s/Q_t = shunt fraction; PEEP = positive end-expiratory pressure; P_{plat} = plateau pressure; V_t = tidal volume; LIS = lung injury score; na = not applicable. P (exact if < 0.10): [1]P=0.000, [2]P=0.01, [3]P=0.04, [4]P=0.05, [5]P=0.07, [6]P=0.08, [7]P=0.10, [8]P=na

DISCUSSION

Our study, employing simultaneous and independent measures of edema, permeability, radiography, mechanics and gas exchange in the lungs, suggests that these indicators do not well interrelate, in patients after cardiopulmonary bypass

surgery without overt cardiac failure. In contrast, it suggests that edema is caused by a low COP rather than increased permeability and that atelectasis better explains the pulmonary radiographic abnormalities and need for PEEP and F_iO_2 to maintain oxygenation than increased permeability pulmonary edema. Hence, our findings may have therapeutic implications, since atelectasis would be treated by altering ventilatory settings and opening the lungs, rather than with help of diuretics to attenuate edema (32). Even though we did not actively attempt to recruit the lungs of patients, most of them had an uneventful recovery, except for a relatively prolonged duration of mechanical ventilation in patients with moderate to severe pulmonary edema.

The frequency of EVLW elevations in our patients agrees with the literature, documenting slight and transient rises in EVLW and pulmonary edema after cardiac surgery, even though the causes and consequences remained unclear (6,8-10,12,14,15). In other studies, however, the EVLW was normal (7,11,13,19,20,23,26). Boldt et al. (9) described that accumulation of EVLW particularly occurred in elderly (>70 years of age) and not in younger patients after cardiac surgery and Buhre et al. (16) described pronounced elevations of EVLW after mitral valvular as opposed to coronary artery surgery. These patient-bound factors did not appear to predispose to pulmonary edema in our study, however, partly because we excluded patients undergoing mitral valve replacement and with overt cardiac failure.

Our data suggest that, after cardiac surgery, a low COP, independently of hydrostatic pressure factors and permeability, contributes to an elevated EVLW, as suggested before on the basis of a calculated rather than measured COP (6,8). Apparently, increased permeability, i.e. an elevated PLI, contributed less to a rise in EVLW than a low COP, thus arguing against a predominant role of a pro-inflammatory response to bypass surgery to edema formation in the lungs (19,25,27). Indeed, even in ALI evoked by oleic acid in dogs, increased permeability may only partially explain pulmonary edema (36). Conversely, hypoproteinemia has been associated with ARDS (37) and acute diastolic heart failure (38), so that a low COP may contribute to pulmonary edema of both cardiogenic and non-cardiogenic origins. As for the PLI (28), the reproducibility of EVLW measurements may be within 10% (17), so that measurement errors cannot account for the lack of a direct correlation between PLI

and EVLW, thereby offering no explanation for the inverse relation either, unless reflecting two populations, one with elevated EVLW and normal PLI and the other with normal EVLW and elevated PLI. The EVLW as a measure of pulmonary edema may be confounded by areas with edema that are underperfused, thereby escaping detection by the thermal-dye technique and perhaps contributing to the inverse relation between EVLW and PLI (10,29). However, CI did not relate to EVLW or to PLI in our study, so that the CI cannot be the source of the inverse relation between EVLW and PLI. Perfusion-dependent EVLW may also mainly apply to direct forms of lung injury, rather than indirect forms (29,36), as in the current study. Boldt et al. (10) demonstrated that the EVLW measurement is independent of CI, after cardiac surgery. A final limitation of our study is that the PLI, EVLW and atelectasis are assessed at differing places in the lung in a relatively small number of patients, and that the PLI may be subject to sampling error, even though an inflammatory increase of permeability might be expected to be homogeneous. A potential perfusion limitation of EVLW and PLI in atelectatic areas may, otherwise, also explain the tendency for lower oxygenation and higher frequency of atelectasis in patients with low EVLW or low PLI. Although a CT scan could overcome some of the limitations mentioned, direct and independent measurements of edema, permeability and atelectasis, as done in this study, cannot be performed by CT (30,31).

The fall in plasma COP after cardiac surgery is partly determined by priming of the cardiopulmonary bypass and administration of non-protein colloids during surgery (26,33). Lumb (11) suggested that priming the system with albumin or hydroxyethyl starch ameliorated a postoperative increase in EVLW. Hoeft et al. (12) observed that EVLW increased in patients on bypass primed with Ringer's lactate but not if primed with albumin solution, but were not able to reproduce these findings in patients undergoing mitral valve replacement (16). Eising et al. (18) used a hyperoncotic (10%) hydroxyethyl starch solution to prime the cardiopulmonary bypass circuit and found less accumulation of EVLW after surgery than when the circuit had been primed by saline. We used gelatin solution to partially prime the circuit (26,33) and this may have been insufficient to prevent a fall in COP and rise in EVLW in some patients. Otherwise, the EVLW/PBV and EVLW/ITBV have been advocated as measures of

pulmonary permeability (19,29,34). Our results indicate that the ratio of EVLW to blood volumes may also rise upon a fall in COP. Finally, a supranormal EVLW did not correlate with alveolar opacities on chest radiography, increased shunt fraction or a low oxygenation ratio, and, indeed, a poor correlation between (changes in) radiographic opacities, gas exchange and EVLW has been observed previously, unless patients with overt cardiac failure are included (11,13,26,29,39). Indeed, considerable lung edema (EVLW >10 mL/kg) must develop before becoming evident on the chest radiograph and impairing gas exchange (6,7,11,13-15,18,39).

That the CVP better predicted EVLW than the PCWP, in conjunction with the COP, may relate to the small numbers of the latter or greater importance of the former. Indeed, systemic venous pressure is the back pressure for lymphatic flow from the lungs, so that an elevated pressure contributes to pulmonary edema, evoked by increased permeability, increased hydrostatic pressures, or both (40). The COP-PCWP gradient has been proposed as the intravascular filtration pressure linked to development of pulmonary edema, even though the level of the effective hydrostatic filtration pressure is somewhere between the MPAP and the PCWP and may be relatively independent of PCWP (6,8,11,12,26,34,38). Our data suggest the COP and CVP as the main determinants of edema in cardiac surgical patients, and the gradient incorporates measures of intravascular filling, filtration and outflow pressure for pulmonary edema. In any case, the lower cardiac filling pressures in the LIS <1 than LIS >1 group could be largely explained by differences in PEEP.

The ARDS prevalence after cardiac surgery in our study conforms with that reported in the literature, between 0.5 and 2.5% (1,2). Since the EVLW was doubled, the PLI was normal in the patient meeting LIS criteria for ARDS (35) and the PLI is uniformly elevated in ARDS (4,28), we cannot exclude that the patient suffered from overhydration rather than ARDS. Conversely, our data suggest that in moderately severe forms of lung injury after cardiac surgery, in which an elevated PLI can be demonstrated, the increased permeability that is believed to result from the injury following bypass-associated ischemia, reperfusion and a proinflammatory response (3-5,19,25,27), does not translate into greater edema formation and lower oxygenation

than in patients with normal postoperative permeability, even though the prevalence of an elevated PLI after cardiac surgery agrees with previous studies (3-5).

Our data may imply that radiographic, mechanical and gas exchange abnormalities, expressed in the LIS (35), are not, wholly or in part, the result of pulmonary permeability or edema. In contrast, we can largely attribute the radiographic and gas exchange abnormalities to postoperative atelectasis, particularly common in the left lower lung lobe, as judged from the predominant location of opacities on the postoperative chest radiograph, and leading to alveolar collapse, a fall in lung volume and increased shunt fraction (30). This may confirm and extent studies by other investigators, reporting that CT scanning of patients 20 h post cardiac surgery revealed basal opacities suggestive for atelectasis in the absence of edema, thereby increasing the shunt fraction (21). Lung collapse during cardiopulmonary bypass may have contributed in our patients. Moreover, the low postoperative compliance agrees with the literature but did not relate to edema, in agreement with some but not with other authors, even though the fall in compliance after cardiac surgery is at least as great for the lungs as for the chest wall (15,22-24). The inverse association between PLI on the one hand and PEEP and compliance on the other can be explained by an underlying inflammatory response (25,27). The cause of a low compliance remains otherwise unclear and cannot be directly attributed to atelectasis either, suggesting a major influence by surgery and anesthesia (15,21-24,30). Finally, our data do not suggest that edema contributed to atelectasis by gravitational forces, with a tendency for lower EVLW in patients with than without atelectasis.

In conclusion, mild pulmonary edema is relatively common shortly after cardiopulmonary bypass surgery, even in the absence of cardiac failure, and is mainly attributable to a low COP, irrespective of increased permeability in about half of patients. It may prolong mechanical ventilation if >10 mL/kg. However, the pulmonary radiographic, gas exchange and mechanical abnormalities are poor indicators of increased pulmonary permeability and edema, so that the former may be largely attributable to atelectasis.

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REFERENCES

1. Fowler AA, Hamman RF, Good JT, Benson KN, Barid M, Eberle DJ, Petty TL, Hyers TM. Adult respiratory distress syndrome: risk with common predispositions. Ann Intern Med 1983; 98: 593-597
2. Milot J, Perron J, Lacasse Y, Létourneau L, Cartier PC, Maltais F. Incidence and predictors of ARDS after cardiac surgery. Chest 2001; 119: 884-888
3. Macnaughton PD, Braude S, Hunter DN, Denison DM, Evans TW. Changes in lung function and pulmonary capillary permeability after cardiopulmonary bypass. Crit Care Med 1992; 20: 1289-1294
4. Raijmakers PGHM, Groeneveld ABJ, Schneider JA, Teule GJJ, Van Lingen A, Eijsman L, Thijs LG. Transvascular transport of ^{67}Ga in the lungs after cardiopulmonary bypass surgery. Chest 1993; 104: 1825-1832
5. Sinclair DG, Haslam PL, Quinlan GJ, Pepper JR, Evans TW. The effect of cardiopulmonary bypass on intestinal and pulmonary endothelial permeability. Chest 1995; 108: 718-724
6. Byrick RJ, Kay JC, Noble WH. Extravascular lung water accumulation in patients following coronary artery surgery. Canad Anaesth Soc J 1977; 24: 332-345
7. Sivak ED, Starr NJ, Graves JW, Cosgrove DM, Borsh J, Estafanous FG. Extravascular lung water values in patients undergoing coronary artery bypass surgery. Crit Care Med 1982; 10: 593-596
8. Klancke KA, Assey ME, Kratz JM, Crawford FA. Postoperative pulmonary edema in postcoronary artery bypass graft patients. Relationship of total serum protein and colloid oncotic pressures. Chest 1983; 84: 529-534
9. Boldt J, von Bormann B, Kling D, Mulch J. Age and cardiac surgery. Influence on extravascular lung water. Chest 1987; 91: 185-189
10. Boldt J, Kling D, von Bormann B, Scheld HH, Hempelmann G. Influence of cardiac output on thermal-dye extravascular lung water (EVLW) in cardiac patients. Intensive Care Med 1987; 13: 310-314
11. Lumb PD. A comparison between 25% albumin and 6% hydroxyethyl starch solutions on lung water accumulation during and immediately after cardiopulmonary bypass. Ann Surg 1987; 206: 210-213
12. Hoeft A, Korb H, Mehlhorn U, Stephan H, Sonntag H. Priming of cardiopulmonary bypass with human albumin or Ringer lactate: effect on colloid osmotic pressure and extravascular lung water. Br J Anaesth 1992; 66: 73-80

13. Hachenberg T, Tenling A, Rothen HU, Nystrom SO, Tydén H, Hedenstierna G. Thoracic intravascular and extravascular fluid volumes in cardiac surgical patients. Anesthesiology 1993; 79: 976-984
14. Louagie Y, Gonzalez E, Jamart J, Bulliard G, Schoevaerdts J-C. Postcardiopulmonary bypass lung edema. A preventable complication? Chest 1993; 103: 86-95
15. Gilbert TB, Barnas GM, Sequeira AJ. Impact of pleurotomy, continuous positive airway pressure, and fluid balance during cardiopulmonary bypass on lung mechanics and oxygenation. J Cardiothorac Vasc Anesth 1996; 10: 844-849
16. Buhre W, Hoeft A, Schorn B, Weyland A, Scholz M, Sonntag H. Acute effects of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass. Br J Anaesth 1997; 79: 311-316
17. Gödje O, Peyerl M, Seebauer T, Dewald O, Reichart B. Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function. Chest 1998; 113: 1070-1077
18. Eising GP, Niemeyer M, Günther T, Tassani P, Pfauder M, Schad H, Lange R. Does a hyperoncotic cardiopulmonary bypass prime affect extravascular lung water and cardiopulmonary function in patients undergoing coronary artery bypass surgery? Eur J Cardiothorac Surg 2001; 20: 282-289
19. Honoré PM, Jacquet LM, Beale RJ, Renauld J-C, Valadi D, Noirhomme P, Goenen M. Effects of normothermia versus hypothermia on extravascular lung water and serum cytokines during cardiopulmonary bypass: a randomized, controlled trial. Crit Care Med 2001; 29: 1903-1909
20. Von Spiegel T, Giannaris S, Wietasch GJ, Schroeder S, Buhre W, Schorn B, Hoeft A. Effects of dexamethasone on intravascular and extravascular fluid balance in patients undergoing coronary bypass surgery with cardiopulmonary bypass. Anesthesiology 2002; 96: 827-834
21. Tenling A, Hachenberg T, Tydén H, Wegenius G, Hedenstierna G. Atelectasis and gas exchange after cardiac surgery. Anesthesiology 1998; 89: 371-378
22. Polese G, Lubli P, Mazzucco A, Luzzani A, Rossi A. Effects of open heart surgery on respiratory mechanics. Intensive Care Med 1999; 25: 1092-1099
23. Babik B, Asztalos T, Peták F, Deák ZI, Hantos Z. Changes in respiratory mechanics during cardiac surgery. Anesth Analg 2003; 96: 1280-1287
24. Roosens C, Heerman J, De Somer F, Caes F, Van Belleghem Y, Poelaert JI. Effects of off-pump coronary surgery on the mechanics of the respiratory system, lung, and chest wall: comparison with extracorporeal circulation. Crit Care Med 2002; 30: 2430-2437
25. Ng CSH, Wan S, Yim APC, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest 2002; 121: 1269-1277
26. Karanko MS, Klossner JA, Laaksonen VO. Restoration of volume by crystalloid versus colloid after coronary artery bypass: hemodynamics, lung water, oxygenation, and outcome. Crit Care Med 1987; 15: 559-566

27. Massoudy P, Zahler S, Backer BF, Braun SL, Barankay A, Meisner H. Evidence for inflammatory responses of the lungs during coronary artery bypass grafting with cardiopulmonary bypass. Chest 2001; 119: 31-36
28. Groeneveld ABJ. Radionuclide assessment of pulmonary microvascular permeability. Eur J Nucl Med 1997; 24: 449-461
29. Groeneveld ABJ, Verheij J. Is pulmonary edema associated with a high extravascular thermal volume? Crit Care Med 2004; 32: 899-901
30. Magnusson L, Spahn DR. New concepts of atelectasis during general anaesthesia. Br J Anaesth 2003; 91: 61-72
31. Drummond GB. Computed tomography and pulmonary measurements. Br J Anaesth 1998; 80: 665-671
32. Dyhr T, Nygård E, Laursen N, Larsson A. Both lung recruitment maneuver and PEEP are needed to increase oxygenation and lung volume after cardiac surgery. Acta Anaesthesiol Scand 2004; 48: 187-197
33. Jansen PGM, Te Veldhuis H, Wildevuur WR, Huybregts MAJM, Bulder ER, van der Spoel HI, Sturk A, Eijsman L, Wildevuur CRH. Cardiopulmonary bypass with modified gelatin and heparin-coated circuits. Br J Anaesth 1996; 76: 13-19
34. Matejovic M, Krouzecky A, Rokyta R Jr, Novak I. Fluid challenge in patients at risk for fluid loading-induced pulmonary edema. Acta Anaesthesiol Scand 2004; 49: 69-73
35. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138: 720-723
36. Schuster DP, Haller J. A quantitative correlation of extravascular lung water accumulation with vascular permeability and hydrostatic pressure measurements: a positron emission tomography study. J Crit Care 1990; 5: 161-168
37. Arif SK, Verheij J, Groeneveld ABJ, Raijmakers PGHM. Hypoproteinemia as a marker of acute respiratory distress syndrome in critically ill patients with pulmonary edema. Intensive Care Med 2002; 28: 310-317
38. Arquès S, Ambrosi P, Gélisse R, Luccioci R, Habib G. Hypoalbuminemia in elderly patients with acute diastolic heart failure. J Am Coll Cardiol 2003; 42: 712-716
39. Baudendistel L, Shields JB, Kaminski DL. Comparison of double indicator thermodilution measurements of extravascular lung water (EVLW) with radiographic estimation of lung water in trauma patients. J Trauma 1982; 22: 983-988
40. Allen SJ, Drake RE, Katz J, Gabel JC, Laine GA. Elevation of superior vena caval pressure increases extravascular lung water after endotoxemia. J Appl Physiol 1987; 62: 1006-1009

CHAPTER 3

Increased pulmonary capillary permeability and extravascular lung water after major vascular surgery. Effect on radiography and ventilatory variables?

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ABSTRACT

Questions of the study. To reveal the pathogenesis of pulmonary ventilatory and radiographic abnormalities in patients after major vascular surgery.

Patients and methods. Sixteen mechanically ventilated patients without heart failure were studied, within three hours after major vascular surgery. We measured extravascular lung water (EVLW), intrathoracic (ITBV), global end-diastolic (GEDV) and pulmonary (PBV) blood volumes, ^{67}Ga-transferrin pulmonary leak index (PLI), and ventilatory and radiographic variables. The latter allowed computation of the lung injury score (LIS) as a measure of lung injury.

Results. The EVLW was elevated (>7 mL/kg) in 5/16 (31%) of patients, while the PLI was elevated in 11/16 (69%) and a supranormal EVLW was associated with a high PLI and higher EVLW relative to ITBV or PBV. Patients arbitrarily divided into those with a >1 and ≤1 LIS differed in the factors composing the score as well as in EVLW divided by PBV. A LIS >1 was associated with a longer duration of mechanical ventilation.

Answer to the question. Our data suggest that mild, subclinical, pulmonary edema is relatively common after major vascular surgery, and mainly caused by increased pulmonary capillary permeability, in the absence of overt heart failure. However, permeability edema only partially contributes to postoperative LIS and need for mechanical ventilation, suggesting a major contribution by atelectasis.

INTRODUCTION

Complications of major vascular surgery include lung gas exchange and mechanical disturbances, and the need for prolonged mechanical ventilation after surgery (1-7). There is ample experimental evidence to suggest that lower body or gut ischemia/reperfusion (I/R) releases a wide variety of humoral and cellular mediators contributing to lung vascular damage (5,8). In humans, we demonstrated before that the permeability to intravenously injected and ^{67}Ga- or ^{111}In-labeled transferrin is increased in the lungs directly but not remotely after aortic surgery, as compared to preoperative values and probably associated with a proinflammatory response originating from the I/R area and affecting the lungs (7,9,10). This was accompanied by subtle lung gas exchange, mechanical and radiographic abnormalities, but a relation of the latter phenomena with release of inflammatory mediators and increased permeability could not be established (9,10). Nevertheless, increased permeability might contribute to a postoperative elevation of EVLW observed in some patients, since pulmonary fluid accumulation may only partially relate to a high hydrostatic and/or low colloid osmotic pressures (1,2,11). However, lung gas exchange, mechanical and radiographic variables may only partially relate to EVLW in critically ill patients (4,12,13). A postoperative increase in elastance or a decrease in compliance may thus relate to postoperative pulmonary vascular congestion or atelectasis rather than edema (4,6,14). Insight into the pathogenesis and interrelations of pulmonary abnormalities after major vascular surgery and I/R could help in designing preventive or therapeutic measures beyond the current practise to mechanically ventilate patients until gas exchange has recovered and extubation can be carried out (4,6).

The current study was thus performed to elucidate the mechanisms of pulmonary ventilatory and radiographic abnormalities in relation to edema and increased capillary permeability, in patients after major vascular surgery and I/R, in the absence of heart failure.

PATIENTS AND METHODS

This study is a single-center observational study. The study was approved by the Ethical Committee of the Vrije Universiteit Medical Center. Written informed consent was obtained in each of the 16 study patients, before planned laparotomy for major vascular surgery. The inclusion criteria, judged when the patients arrived at the intensive care unit (ICU), were absence of heart failure, defined as a pulmonary capillary wedge pressure (PCWP) at or below 15 mm Hg in the presence of a pulmonary artery catheter (n=3) or a central venous pressure (CVP) at or below 12 mm Hg in the presence of a central venous catheter, and a (transpulmonary) cardiac index greater than 2.0 L/min/m^2. Patients were thus only included if they had arterial and pulmonary artery/central venous catheters. Exclusion criteria were: age >79 years, pregnancy, and a life expectancy of less than 24 hours. On the day of the surgery, anesthesia was induced with sufentanil 3 µg/kg i.v., pancuronium 0.1 mg/kg i.v. and midazolam 0.1 mg/kg i.v., and maintained with a continuous infusion of propofol. Radial artery, central venous or pulmonary artery catheters (n=3) were inserted for hemodynamic measurements and blood sampling. After tracheal intubation, the lungs were ventilated with a tidal volume of 8 mL/kg resulting in an end-tidal CO_2 concentration between 4 and 5% using an O_2-air mixture with an inspiratory O_2 concentration of minimum 40%, depending on arterial PO_2. A positive end-expiratory pressure (PEEP) of 5 cm H_2O was applied, without recruitment maneuvers. Crystalloid and colloid fluids were infused, when necessary in the presence of low systemic and filling pressures. If volume therapy did not suffice, vasoactive drugs were given. In the presence of a hemoglobin concentration less than 6 mmol/L, packed red blood cells were infused. Preoperative use of aspirin and excessive bleeding prompted for administration of donor platelet concentrates. At the end of surgery, a 4F introducing sheath (Arrow, Reading, USA) was inserted into the femoral artery, when feasible, for use in the study protocol. The aortic clamping time was recorded.

Study protocol. At the arrival of the patient in the ICU, the patient was connected to the ventilator (Evita 3, Dräger, Lübeck, Germany) and volume-controlled ventilation was started with similar settings as during surgery. The study protocol was started within three hours after arrival. Demographics were recorded, including the acute

physiology and chronic health evaluation (APACHE-II) score and baseline (t=0 min) measurements of hemodynamics were performed. Pressures were measured after calibration and zeroing to atmospheric pressure at midchest level (Tramscope^{R}, Marquette, Wisc., USA). Mean pulmonary artery pressure, CVP and, after balloon inflation, the PCWP were taken at end-expiration, with patients in the supine position. The colloid osmotic pressure (COP) was measured by a membrane osmometer (Osmomat 050, Gonotex, Berlin, Germany, molecular cut-off at 20 kDa), in arterial blood samples. Arterial and mixed (n=3) or central venous (n=13) samples were taken for determination of PO_2 and O_2 saturation, for calculation of the oxygenation ratio (arterial PO_2 [P_aO_2] over inspiratory O_2 fraction [F_iO_2]) and shunt fraction Q_s/Q_t (Rapidlab 865, Bayer Diagnostics, Tarrytown, NY, USA), according to standard formulae. The F_iO_2, tidal volume, plateau inspiratory pressure and positive end-expiratory pressure (PEEP, cm H_2O) were taken from the ventilator. A chest radiograph was taken. Doses of vasoactive drugs were recorded.

Transpulmonary thermal-dye dilution. The measurement involves a central venous injection of 15 mL of ice-cold indocyanine green (ICG), 1 mg/mL D5W. The thermal-dye dilution curve was obtained at the femoral artery (COLD Z-021, Pulsion Medical Systems, Munich, Germany), with help of a 3F catheter (PV 2024, Pulsion Medical Systems, Munich, Germany), introduced via the introducing sheath. This allowed calculation of the transpulmonary thermodilution cardiac output and both the thermal as well as the ICG distribution volume, the intrathoracic blood volume (ITBV). The difference between the volumes is the extravascular thermal volume in the lungs as an estimate of extravascular lung water (EVLW, normal <7 mL/kg), as described and validated before (13,15,16). The pulmonary blood volume (PBV) is derived from cardiac output and the downslope time of the ICG dilution, as described before (15). The global end-diastolic volume (GEDV) is derived from intrathoracic thermal volume minus pulmonary thermal volume, the latter derived from the downslope time of thermal dilution. The normal ratio of EVLW/ITBV (mL/mL) is 0.2 to 0.3 and the normal EVLW/PBV ratio is about 1. The indices have been proposed to reflect permeability (15,17). Measurements were done in duplicate, irrespective of the ventilatory cycle, and averaged. GEDV and cardiac output were indexed to body surface area calculated from weight and height, while EVLW was indexed to body weight.

PLI. The PLI was measured according to previously described methods (9,10). In brief, autologous red blood cells were labeled with ^{99m}Tc (11 MBq, physical half-life 6h; Mallinckrodt Diagnostica, Petten, The Netherlands), using a modified in vitro method, to correct for blood volume under the probe. Ten minutes after administration of pyrophosphate (TechneScan, Mallinckrodt Medical, Petten, The Netherlands), 10 mL of blood was obtained and equilibrated with ^{99m}Tc. Ten minutes later the blood was reinjected. Transferrin was labeled in vivo, following i.v. injection of ^{67}Ga-citrate, 4.5 MBq (physical half-life 78 h; Mallinckrodt Diagnostica, Petten, The Netherlands). Patients were in the supine position and two cesium-iodide scintillation detection probes (Eurorad C.T.T., Strasburg, France) were positioned over the right and left lung apices. Starting at the time of injection of ^{67}Ga, radioactivity was detected every minute, during 30 minutes. The count rates were corrected for background radioactivity, physical half-life and spill-over, and expressed as counts per minute (CPM) per lung field. Until 30 minutes after ^{67}Ga injection, blood samples (2 mL aliquots) were taken. Each blood sample was weighed and radioactivity was determined with a single well well-counter, corrected for background, spillover, and decay (LKB Wallac 1480 Wizard, Perkin Elmer, Life Science, Zaventem, Belgium). Results were expressed as CPM/g. For each blood sample, a time-matched CPM over each lung was taken. A radioactivity ratio was calculated, ($^{67}Ga_{lung}$/$^{99m}Tc_{lung}$)/($^{67}Ga_{blood}$/$^{99m}Tc_{blood}$), and plotted against time. The PLI was calculated, using linear regression analysis, from the slope of increase of the radioactivity ratio divided by the intercept, to correct for physical factors in radioactivity detection. By taking pulmonary blood volume and thus presumably surface area into account, the radioactivity ratio represents the ratio of extravascular versus intravascular ^{67}Ga radioacitivity. The PLI represents the transport rate of ^{67}Ga from the intravascular to the extravascular space of the lungs and is therefore a measure of pulmonary capillary permeability (9,10). The values for both lungs were averaged. The upper limit of normal for the PLI is 14.1 x 10^{-3}/min and the measurement error is about 10% (9). The value is typically elevated three- to fourfold in case of acute respiratory distress syndrome (9).

Radiography and the lung injury score. The lung injury score (LIS) was calculated from the number of quadrants on the chest radiograph with densities, the PEEP level, the P_aO_2/F_iO_2 and the dynamic total respiratory compliance (18). The latter was

calculated from tidal volume/(plateau pressure-PEEP), mL/cm H_2O. The chest radiograph was scored by a consultant radiologist, blinded to the study, who evaluated the number of quadrants with alveolar densities, ranging from 1 to 4. The LIS ranges between 0 (no injury) to 4, with a value above 2.5 indicative of ARDS and between 0 and 2.5 of ALI (18).

Statistical analysis. We arbitrarily created groups with normal and supranormal EVLW (>7 mL/kg) and with LIS below and above 1. Comparisons were made with the Fisher's exact test and the non-parametric Mann-Whitney U test. The non-parametric Spearman correlation coefficient was used to express relations. Data were summarized as median (range). All tests were two-sided and a $P<0.05$ was considered statistically significant.

Table 1. Patient characteristics

Age, year	64 (51-75)
Sex, M/F	13/3
Prior disease	
chronic obstructive pulmonary disease	5
cardiac disease	6
Type of surgery	
abdominal aortic aneurysm repair	12
coeliac/mesenteric reconstruction	4
Aortic clamp time (n=12), min	88 (45-105)

Median (range) or number of patients, where appropriate.

RESULTS

Table 1 describes the characteristics of the patients, who all survived to discharge, and Table 2 hemodynamic variables. The EVLW was elevated (>7 mL/kg) in 5/16 (31%) of patients, while the PLI was elevated in 11/16 (69%). An elevated EVLW was associated with an elevated ratio of EVLW to ITBV or PBV as well as with a higher PLI. EVLW directly correlated to GEDV index (r_s=0.58, $P<0.05$). Table 3 shows that all patients had ALI, since P_aO_2/F_iO_2 (n >480) and compliance (n >80 mL/cm H_2O) had decreased, among others. There was a difference in EVLW/PBV between high and low LIS patients. The latter also differed in the components of the LIS, including gas exchange, mechanical and radiographic abnormalities, while EVLW did not relate to

the components. A LIS >1 was associated with prolonged need for mechanical ventilatory support. Conversely, aortic clamping time was higher and tidal volume and compliance were lower in patients with high versus low PLI ($P<0.05$).

DISCUSSION

Our study suggests that an elevated EVLW is common after I/R associated with major vascular surgery and that this is mainly caused by increased capillary permeability. However, many of the ventilatory and radiographic abnormalities could be explained by atelectasis rather than mild permeability edema, since the PLI and EVLW did not differ among LIS groups.

Table 2. Hemodynamic variables

	EVLW ≤7 n=11	>7 mL/kg n=5	LIS ≤1 n=9	>1 n=7
Heart rate, b/min	67 (46-90)	70 (55-87)	66 (46-74)	68 (63-90)
Mean arterial pressure, mm Hg	73 (63-89)	87 (68-113)	77 (66-113)	72 (63-107)
MPAP, mm Hg	15 (13,17)	21	17	17 (13,21)
Central venous pressure, mm Hg	3 (1-8)	4 (0-9)	3 (0-8)	4 (1-9)
PCWP, mm Hg	5 (4,6) (n=2)	10 (n=1)	4 (n=1)	8 (6,10) (n=2)
Cardiac index, L/min/m^2	3.2 (2.1-4.5)	3.5 (2.6-4.7)	3.2 (2.7-4.5)	3.1 (2.1-4.7)
GEDV index, mL/m^2	897 (629-1168)	1065 (547-1149)	898 (547-1168)	903 (689-1149)
Colloid osmotic pressure, mm Hg	16 (13-20)	14 (13-19)	16 (13-17)	16 (14-20)
Dopamine	8	3	6	5
Nitroglycerin	7	3	4	6

Median and range or number of patients where appropriate; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; GEDV = global end-diastolic volume.

We have shown before that, directly after aortic surgery associated with I/R, the PLI increases two- to threefold, at least temporarily (9,10). This increase was accompanied by an elevated LIS, but there was no relation between the PLI and the LIS or its components (9,10). The current study supplements the former (9,10) by documenting an increased EVLW, even though preoperative values were not taken in the same patients. Thus, our current study suggests that an increase in EVLW is associated with mildly elevated alveolocapillary permeability, as in animal studies (8), for a given

hydrostatic pressure. Indeed, EVLW related to GEDVI, suggesting a contribution by hydrostatic factors as observed during sepsis (16), since edema formation by increased permeability may be promoted by hydrostatic factors (13). In any case, the data are consistent with absence of overt heart failure, by virtue of the inclusion criteria.

Table 3. Respiratory variables

	EVLW ≤7 n=11	>7 mL/kg n=5	LIS ≤1 n=9	>1 n=7
EVLW, ml/kg	5.7 (2.5-6.5)	8.2 (7.2-13.8)[na]	5.8 (2.5-12.7)	6.2 (5.2-13.8)
EVLW/ITBV, mL/mL	0.22 (0.09-0.28)	0.33 (0.21-0.42)[*]	0.21 (0.09-0.37)	0.27 (0.21-0.42)
EVLW/PBV, mL/mL	1.1 (0.4-1.6)	0.9 (1.2-2.7)[**]	1.1 (0.4-1.9)	1.5 (1.1-2.6)[*]
Pulmonary leak index, 10^{-3} /min	14 (11-32)	32 (24-81)[**]	21 (11-81)	22 (12-32)
P_aO_2, mm Hg	137 (93-189)	104 (76-220)	158 (93-220)	124 (76-161)
P_aCO_2, mm Hg	37 (31-46)	4 (31-41)	35 (31-46)	36 (31-41)
F_iO_2	0.4 (0.4-0.5)	0.5 (0.4-0.6)	0.4 (0.4-0.5)	0.5 (0.5-0.6)[***]
P_aO_2/F_iO_2	290 (186-461)	208 (127-537)	385 (186-537)	248 (127-316)[**]
Q_s/Q_t, %	21 (6-45)	25 (4-10)	16 (4-45)	25 (21-40)[*]
Plateau pressure, cm H_2O	20 (12-23)	19 (15-22)	15 (12-21)	21 (15-23)[**]
PEEP, cm H_2O	6 (5-9)	7 (5-10)	5 (5-9)	7 (5-10)
Tidal volume, mL	655 (450-730)	600 (430-708)	635 (430-730)	650 (500-708)
Compliance, mL/cm H_2O	54 (28-94)	53 (31-71)	63 (31-94)	46 (28-71)
Radiographic alveolar densities, number of quadrants	1 (0-3)	1 (0-2)	0 (0-2)	2 (1-3)[**]
Lung injury score	0.7 (0.2-1.7)	1.5 (0.2-2.0)	0.7 (0.2-1.0)	1.5 (1.25-2.00)[na]
Duration of ventilation, h	12 (1-87)	9 (7-49)	6 (1-32)	20 (9-87)[*]

Median and range or number of patients where appropriate; EVLW = extravascular lung water; ITBV = intrathoracic blood volume; PBV = pulmonary blood volume; P_aO_2 = arterial PO_2; F_iO_2 = inspiratory O_2 fraction; Q_s/Q_t = pulmonary venous admixture; PEEP = positive end-expiratory pressure; [*]P<0.05; [**]P<0.01;[***]P<0.005; [na] not applicable. To convert mm Hg to kPA, divide by 7.3.

Patients with a high LIS had an elevated EVLW as fraction of PBV, suggesting that increased permeability was in part responsible for some of the ventilatory and radiographic abnormalities. However, our data also suggest that increased permeability edema only partially explained the postoperative increase in LIS, so that unmeasured factors including atelectasis must have contributed. Indeed, atelectasis is common in anesthetized and mechanically ventilated patients with prior normal lungs, and may be difficult to discern on routine supine chest radiographs rather than CT scans, and may persist for some time after surgery (14). We did not perform CT

scanning because of the transport involved. Moreover, CT scanning does not unequivocally differentiate between edema and atelectasis. Finally, our patients had a relatively uneventful postoperative course, allowing detubation on the first postoperative day, again arguing in favor of recruitable atelectasis.

There was no relation between compliance on the one hand and EVLW or ITBV/PBV on the other, suggesting that atelectasis was a major cause of a low postoperative compliance (6,14). We did not separate total respiratory compliance in lung and chest wall compliances in the absence of pleural pressure measurements. Nevertheless, both lung and chest wall elastances may increase and compliances decrease during and after aortic surgery (6). The lack of relation between radiographic densities and EVLW may agree with the literature (12,13), and this may thus point again to, mainly basal, atelectatic areas.

In conclusion, our results suggest that, directly after major vascular surgery-associated I/R, mild and 'subclinical' pulmonary edema formation is common and mainly caused by increased permeability, in the absence of overt heart failure. However, increased permeability edema only partly contributes to gas exchange, mechanical and radiographic abnormalities, suggesting atelectasis as a contributory factor to lung injury and need for mechanical ventilatory support, after surgery.

REFERENCES

1. Virgilio RW, Rice CL, Smith DE, et al. Crystalloid vs. colloid resuscitation: is one better? A randomized clinical study. Surgery 1979; 85: 129-139
2. Shires GT, Peitzman AB, Albert SA, et al. Response of extravascular lung water to intraoperative fluids. Ann Surg 1983; 197: 515-518
3. Vodinh J, Bonnet F, Touboul C, Lefloch JP, Becquemin JP, Harf A. Risk factors of postoperative pulmonary complications after vascular surgery. Surgery 1989; 105: 360-365
4. Jayr C, Matthay MA, Goldstone J, Gold WM, Wiener-Kronish JP. Preoperative and intraoperative factors associated with prolonged mechanical ventilation. A study in patients following major abdominal vascular surgery. Chest 1993; 103: 1231-1236
5. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 1995; 82: 1026-1060

6. Volta CA, Ferri E, Marangoni E, et al. Respiratory function after aortic aneurysm repair: a comparison between retroperitoneal and transperitoneal approaches. Intensive Care Med 2003; 29: 1258-1264
7. Adembri C, Kastamoniti E, Bertolozzi I, et al. Pulmonary injury follows systemic inflammatory reaction in infrarenal aortic surgery. Crit Care Med 2004; 32: 1170-1177
8. Iglesias JL, LaNoue JL, Rogers TE, Inman L, Turnage RTH. Physiologic basis of pulmonary edema during intestinal reperfusion. J Surg Res 1998; 80: 156-163
9. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, et al. Transient increase in interleukin-8 and pulmonary microvascular permeability following aortic surgery. Am J Respir Crit Care Med 1995; 151: 698-705
10. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, Teule GJJ, Hack CE. Acute lung injury after aortic surgery: the relation between lung and leg microvascular permeability to ^{111}indium-labelled transferrin and circulating mediators. Thorax 1997; 53: 866-871
11. Skillman JJ, Restall S, Salzman EW. Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. Surgery 1975; 78: 291-303
12. Halperin BD, Feeley TW, Mihm FG, Chiles C, Guthaner DF, Blank NE. Evaluation of the portable chest roentgenogram for quantitating extravascular lung water in critically ill adults. Chest 1985; 88: 649-652
13. Sibbald WJ, Short AK, Warshawski FJ, Cunningham DG, Cheung H. Thermal dye measurements of extravascular lung water in critically ill patients. Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. Chest 1985; 87: 585-592
14. Magnusson L, Spahn DR. New concepts of atelectasis during general anaesthesia. Br J Anaesthesia 2003; 91: 61-72
15. Gödje O, Peyerl M, Seebauer T, Dewald O, Reichart B. Reproducibility of double indicator dilution measurement of intrathoracic blood volume compartments, extravascular lung water, and liver function. Chest 1998; 113: 1070-1077
16. Boussat S, Jacques T, Levy B, et al. Intravascular volume monitoring and extravascular lung water in septic patients with pulmonary edema. Intensive Care Med 2002; 28: 712-718
17. Honore PM, Jacquet LM, Beale RJ, et al. Effects of normothermia versus hypothermia on extravascular lung water and serum cytokines during cardiopulmonary bypass: a randomized, controlled trial. Crit Care Med 2001: 29: 1903-1909
18. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138: 720-723

CHAPTER 4

Impaired oxygenation in sepsis-induced acute lung injury and respiratory distress syndrome: effect of increased permeability edema?

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SUBMITTED

ABSTRACT

Objective. To study the relation between gas exchange abnormalities and increased permeability edema in sepsis-associated acute lung injury/acute respiratory distress syndrome (ALI/ARDS) by pneumonia or an extrapulmonary origin.

Design. A prospective observational study.

Patients. Twenty-two consecutive mechanically ventilated patients with sepsis-related ALI/ARDS from pneumonia (n=12) or extrapulmonary sources (n=10).

Setting. Intensive care unit of an university hospital.

Measurements and results. Protein permeability was assessed non-invasively over the lungs with help of ^{67}Ga-transferrin and ^{99m}Tc-red blood cells (pulmonary leak index PLI, n< 14.1 x 10^{-3}/min) and extravascular lung water (EVLW) by the thermal-dye transpulmonary dilution technique, also allowing assessment of cardiac output. 45% of patients had asymmetric lung injury on plain radiographs, associated with an elevated PLI difference between lungs, while the lung-averaged PLI was above normal in all patients and the EVLW in only 68%. The PLI directly correlated with venous admixture, so that patients with a PLI > 40 x 10^{-3}/min had a higher venous admixture than those with a lower PLI, at similar EVLW. The PLI related to the ratio of EVLW to pulmonary or intrathororacic blood volume (PBV, ITBV). Pneumonia was associated with a high PLI, more extensive radiographic pulmonary densities, higher venous admixture and cardiac index, and lower oxygenation ratio than extrapulmonary sepsis, independently of EVLW (and its ratio to PBV and ITBV).

Conclusion. The data support that in mechanically ventilated patients with sepsis-induced ALI/ARDS, increased venous admixture is better explained by a lung vascular injury than by edema. They also suggest that the vascular injury is greater in pneumonia than in extrapulmonary sepsis.

INTRODUCTION

Acute lung injury (ALI) progressing to acute respiratory distress syndrome (ARDS) during sepsis, a major risk factor for ALI/ARDS, is characterized by pulmonary radiographic and mechanical abnormalities and impaired oxygenation, thought to originate from increased permeability edema following a lung vascular injury. The latter is reflected by an elevated protein permeability, as measured by the non-invasive double radionuclide ^{67}Ga-transferrin pulmonary leak index (PLI) (1-4). During pneumonia and ALI/ARDS, indeed, the PLI may moderately relate to the lung injury score (LIS), which takes the clinical manifestations into account (5), but hardly to its components including impaired oxygenation, while the extent of non-areated tissue on computer tomography (CT) scans may directly relate to venous admixture during ALI/ARDS (6). In the latter studies, however, lung edema was not directly assessed and non-areated tissue could also include consolidation or atelectasis (7). This differentiation can be important from a therapeutic point of view, whereas the role of edema may differ in direct and indirect ALI/ARDS (8,9).

The transpulmonary thermal-dye dilution technique allows estimating extravascular lung water (EVLW), but about one third percent of ALI/ARDS patients may have a normal EVLW, and EVLW may thus poorly correlate with radiographic pulmonary densities (10-12). It is unknown whether this could be attributed in part to inaccessibility of the thermal indicator in direct lung injury, thereby underestimating lung edema (10-17). Radiographic pulmonary densities in the absence of an elevated EVLW could also be explained by consolidation or atelectasis. Moreover, the ratio of EVLW to pulmonary or intrathoracic blood volume (PBV, ITBV), has been proposed as an index of permeability, but this is yet unproven (12,18-20) and the ratio has been shown to be influenced also by a low plasma colloid osmotic pressure, at least after cardiac surgery (21).

To evaluate the contribution of increased permeability, edema and origin of sepsis-induced ALI/ARDS to impaired oxygenation, we measured, in 22 consecutive mechanically ventilated patients in the intensive care unit (ICU) with pneumonia or

extrapulmonary sepsis-induced ALI/ARDS, the EVLW (to PBV and ITBV ratio), the PLI and ventilatory and gas exchange variables (5).

PATIENTS AND METHODS

This is a prospective study, approved by the Ethical Committee of the Vrije Universiteit medical centre, involving 22 consecutive mechanically ventilated patients with sepsis and ALI/ARDS in the ICU, given written informed consent (from patient or relatives), in a 24 month period. The inclusion criteria were the presence of a pulmonary artery (n=3) or central venous catheter (n=19), within 24 hours of meeting criteria for severe sepsis and ALI/ARDS. Severe sepsis was defined by abnormal body temperature (>38 °C, <36 °C), abnormal white blood cell counts (<4, >12 x 10^9/L or >10% immature bands), hypotension and (increasing) need for vasopressor/inotropic therapy, and a clinically evident and microbiologically proven source of infection. ICU-acquired sepsis was defined as sepsis developing after two days in the ICU. ALI was defined by a LIS >0 and ≤2.5 and ARDS by a LIS>2.5 (5), in the absence of overt congestive heart failure or overhydration, defined by a CVP >12 mm Hg or >17 mm Hg if PEEP >15 cm H_2O. Pneumonia was defined by purulent sputum with a positive blood/tracheal aspirate culture, temperature above 38 °C or below 36 °C and recent-onset densities on the chest X-ray. Other origins of sepsis were defined on the basis of clinical signs and symptoms and positive local and/or blood cultures. Exclusion criteria were an age above 79 years, pregnancy and a life expectancy less than 24 hours. Radial artery, central venous and pulmonary artery catheters were inserted for hemodynamic measurements and blood sampling. After tracheal intubation, the lungs were pressure-controlled ventilated with a tidal volume (V_t) of 6-8 mL/kg resulting in an end-tidal CO_2 concentration between 4 and 5%, using an O_2-air mixture and positive end-expiratory pressure of 5 cm H_2O or more, when needed (I:E 1:2). We did not routinely attempt to recruit potential atelectatic areas. Patients were otherwise treated according to our guidelines for hemodynamic optimization, vasopressor/inotropic support with norepinephrine or dopamine, infection control with antibiotics guided by sensitivities of causing microorganisms, and continuous renal replacement techniques when indicated on clinical grounds. The PLI was measured as described previously (1-4). In brief,

autologous red blood cells were labeled with ^{99m}Tc (11 MBq, physical half-life 6h; Mallinckrodt Diagnostica, Petten, The Netherlands). Transferrin was labeled in vivo, following i.v. injection of ^{67}Ga-citrate, 4.5 MBq (physical half-life 78 h; Mallinckrodt Diagnostica, Petten, The Netherlands). Patients were in the supine position and two scintillation detection probes (Eurorad C.T.T., Strasburg, France) were positioned over the right and left lung apices. Starting at the time of injection of ^{67}Ga, radioactivity was detected every minute, during 30 minutes. The count rates were corrected for background radioactivity, physical half-life and spill-over and expressed as counts per minute (CPM) per lung field. Until 30 minutes after ^{67}Ga injection, blood samples (2 mL aliquots) were taken. Each blood sample was weighed and radioactivity was determined with a single well well-counter, corrected for background, spillover and decay (LKB Wallac 1480 WIZARD, Perkin Elmer, Life Science, Zaventem, Belgium). Results were expressed as CPM/g. For each blood sample, a time-matched CPM over each lung was taken. A radioactivity ratio was calculated, ($^{67}Ga_{lung}$/$^{99m}Tc_{lung}$)/($^{67}Ga_{blood}$/$^{99m}Tc_{blood}$), and plotted against time. The PLI was calculated, using linear regression analysis, from the slope of increase of the radioactivity ratio divided by the intercept. The PLI represents the transport rate of ^{67}Ga from the intravascular to the extravascular space of the lungs and is therefore a measure of pulmonary vascular permeability (1-3). The values for both lung fields were averaged, but the difference between the radiographically most affected and least affected side, in case of asymmetric injury, was calculated also. The upper limit of normal for the PLI is 14.1 x 10^{-3}/min and the measurement error is about 10% (1-3). The PLI typically exceeds 40 x 10^{-3}/min in ARDS (1-3).

The EVLW was measured with help of the thermal-dye technique (13,14,22). A 4F introducing sheath (Arrow, Reading, USA) was inserted into the femoral artery, for use in the study protocol, in each patient. A 3F fiberoptic thermodilution catheter was inserted in the femoral artery sheath. Fifteen mL of ice cold indocyanine green (ICG), 1 mg/mL D5W, was injected in a central vein and the thermal-dye dilution curve obtained at the femoral artery (COLD Z-021, Pulsion Medical Systems, Munich, Germany). This allowed calculation of the transpulmonary cardiac output, the intrathoracic blood volume (ITBV), the global end-diastolic volume (GEDV), the pulmonary blood volume

(PBV) and the extravascular thermal volume in the lungs as a measure of EVLW (normal <7-10 mL/kg) (13,14,17,22). EVLW is typically two- to threefold elevated in case of overt (radiographic) pulmonary edema (10,12-14,17,22). The normal ratio of EVLW/ITBV (mL/mL) is 0.2 to 0.3 and the normal EVLW/PBV ratio is about 1, and the indices have been proposed, but not proven, to reflect permeability (12,18,20). Measurements were done in duplicate and averaged. The cardiac output and GEDV were indexed to body surface area (cardiac index, CI; GEDVI) and EVLW to kg. Hemodynamics were included in the study since they may affect pulmonary variables.

The LIS was calculated from the number of quadrants on the chest radiograph with densities, the PEEP level, the arterial PO_2 (P_aO_2)/inspiratory O_2 fraction (F_iO_2) and the total dynamic respiratory compliance (5). The compliance was calculated from tidal volume/(plateau pressure-PEEP), mL/cm H_2O. The chest radiograph was scored by a consultant radiologist, blinded to the study, who evaluated the number of quadrants with alveolar densities, ranging from 0 to 4. Moreover, asymmetric injury and evidence for basal atelectasis were judged.

Protocol. Demographics were recorded, including variables for calculation of the acute physiology and chronic health evaluation (APACHE-II) score, measurements of EVLW, ^{67}Ga-transferrin PLI and hemodynamics were performed, and an anteroposterior chest radiograph was made. Hemodynamic variables were measured after calibration and zeroing to atmospheric pressure at mid-chest level (Tramscope^R, Marquette, Wisc., USA). CVP was taken at end-expiration, with patients in the supine position. Arterial blood samples were obtained for determinations of partial O_2/CO_2 pressures and O_2 saturations (Rapidlab 865, Bayer Diagnostics, Tarrytown, NY, USA, at 37 °C). Mixed (n=3) or central (n=19) venous blood was taken simultaneously for measurement of partial pressures and saturations. Venous admixture was calculated according to standard formulae, with central venous substituting for mixed venous blood in the absence of a PA catheter (23). The plasma colloid osmotic pressure (COP) was measured by a membrane osmometer (Osmomat 050, Gonotex, Berlin, Germany, molecular cut-off at 20 kDa, normal about 24 mm Hg). The F_iO_2, tidal volume, plateau inspiratory pressure and PEEP (cm H_2O) were taken from the ventilator. Doses of vasoactive drugs were recorded. Patients were taken care of by intensive care physicians not involved in the study and followed until extubation and discharge/death

in the ICU. Mortality is ICU mortality.

Statistical analysis. We compared groups with pneumonia and extrapulmonary sepsis, with and without radiographic evidence for atelectasis, and those dichotomised according to relevant values of PLI, EVLW (7 and 10 mL/kg), LIS, asymmetric/ symmetric injury and absence/presence of atelectasis, with help of the non-parametric Mann-Whitney U test for continuous and with help of the Fisher's exact test for categorical data. The Spearman correlation coefficient was used to express relations. The area (AUC) under the receiver-operating characteristic curve (ROC) was evaluated for the predictive value of variables for mortality. Exact P values below 0.10 are given and a $P<0.05$ was considered to indicate statistical significance. All tests were two-sided. Data were summarised as median and range.

Table 1. Patient characteristics

Age, year	59 (45-77)
Sex, M/F	16 (73)/6 (27)
Underlying disease	
cardiac surgery	3 (14)
other surgery	6 (27)
acute pancreatitis	1 (4)
diabetes mellitus	4 (18)
renal insufficiency	1 (4)
malignancy	4 (18)
chronic lung disease	2 (9)
Source of sepsis	
pneumonia	12 (55)
abdominal	4 (18)
urogenital	1 (4)
blood/catheter	2 (9)
other	3 (14)
Culture results	
Blood Gram-	1 (4)
Gram +	5 (23)
fungal	1 (4)
Local* Gram-	7 (32)
Gram +	4 (18)
fungal	4 (18)
ICU-acquired sepsis	7 (32)
APACHE II score	15 (6-23)
Temperature, °C	37.0 (35.4-38.8)
Arterial PCO_2, mm Hg	40 (32-67)
Renal replacement therapy	2 (9)
Vasopressor/inotropic therapy	19 (86)
Interval between admission and study, days	1 (0-41)
Mortality in ICU	7 (32)

Median (range) or number of patients, where appropriate. *When blood-culture negative.

RESULTS

Table 1 describes the patient characteristics and Table 2 hemodynamic and pulmonary data. While only 67% of ALI and 71% of ARDS patients had an elevated EVLW (>7 mL/kg), all patients had a PLI above normal.

ALI versus ARDS. Patients with ALI (LIS≤2.5) and ARDS (LIS>2.5) did not differ in PLI and EVLW, but in oxygenation, which was worse in ARDS, and in PEEP and plateau pressures, which were higher (Table 2). In ARDS patients, the PLI tended to be higher (n=5, above 47 x 10^{-3}/min) during pneumonia than during extrapulmonary sepsis (n=2, below 47 x 10^{-3}/min, P=0.090).

Asymmetric versus symmetric ALI/ARDS. It is shown that the interlung difference in PLI was greater in case of radiographic asymmetric than symmetric lung injury, which otherwise did not differ.

Pneumonia versus extrapulmonary sepsis. Table 3 shows that patients with pneumonia had a higher cardiac output, more radiographic densities, greater venous admixture and lower oxygenation ratio than patients with extrapulmonary sepsis. The frequency of high PLI's was also elevated in the former.

Severely versus moderately elevated PLI. Groups differed in venous admixture and frequency of pneumonia (Table 3).

High versus low EVLW and evidence for basal atelectasis. Patients with EVLW >10 (n=9) or <10 mL/kg (n=13), or with (n=7) and without (n=15) radiographic evidence for basal atelectasis, did not differ in pulmonary variables, except for a lower tidal volume and compliance (P=0.023) in patients with atelectasis.

ICU-acquired versus non-ICU acquired sepsis. In the former group (n=7), the PLI and venous admixture were higher and S_aO_2 was lower than in the latter group (n=15, P=0.047 or lower), while EVLW (and other pulmonary variables) did not differ.

Correlations. The oxygenation ratio inversely correlated (r_s=-0.85, P<0.0001) to venous admixture. There was a direct relation between PLI and venous admixture (r_s=0.42, P=0.050). There was also a direct relation (Fig. 1) between the PLI and the EVLW to PBV or ITBV ratio and the latter to radiographic pulmonary densities, particularly in extrapulmonary sepsis and pneumonia (r_s=0.71, P=0.022, and r_s=0.67, P=0.017 in these subgroups, respectively). In the group as a whole, there were no

statistically significant relations between EVLW (to blood volume ratios), radiographic densities, gas exchange and mechanical abnormalities, nor between PLI and radiographic densities and mechanical abnormalities.

Table 2. ALI/ARDS and radiographic symmetry

	ALI (LIS≤2.5) n=15	ARDS (LIS>2.5) n=7	Asymmetric n=10	Symmetric n=12
Hemodynamic				
HR, /min	104 (46-139)	92 (64-132)	106 (66-139)	86 (46-130)
MAP, mm Hg	75 (61-95)	70 (60-89)	73 (61-95)	73 (60-89)
CVP, mm Hg	6 (0-16)	9 (4-13)[2]	8 (4-16)	6 (0-13)[1]
GEDVI, mL/m^2	884 (556-1446)	818 (652-1106)	904 (591-1447)	788 (556-1196)
CI, L/min/m^2	3.4 (2.3-5.5)	3.7 (2.9-6.6)	3.9 (2.7-6.6)	3.5 (2.3-5.3)
COP, mm Hg	16 (10-20)	17 (15-19)	16 (10-19)	16 (13-20)
Dopamine, mg/h	24 (0-52)	32 (20-56)	28 (0-52)	24 (0-56)
Norepinephrine, mg/h	0.2 (0-1.2)	0 (0-1.0)	0.2 (0-1.2)	0 (0-0.8)
Pulmonary				
PLI, x 10^{-3}/min	56 (17-217)	49 (39-204)	50 (28-217)	53 (17-204)
Difference, %	9 (0-31)	5 (2-29)	11 (5-31)	4 (1-29)[5]
PLI >40 x 10^{-3}/min	10 (67)	6 (86)	7 (70)	9 (75)
EVLW, mL/kg	7.1 (1.9-18.1)	14.9 (4.1-33.9)	9.7 (4.4-21.3)	7.3 (1.9-33.9)
EVLW >10 mL/kg	5 (33)	4 (57)	5 (50)	4 (33)
EVLW/ITBV	0.27 (0.10-0.64)	0.68 (0.13-0.91)	0.30 (0.13-0.85)	0.27 (0.10-0.91)
EVLW/PBV	1.4 (0.5-19.6)	3.4 (0.5-17.3)	1.6 (0.5-7.3)	1.5 (0.5-19.6)
P_aO_2, mm Hg	109 (65-141)	97 (82-108)[4]	97 (65-119)	107 (82-141)
S_aO_2, %	97 (93-99)	97 (94-98)	97 (93-99)	97 (96-98)
F_iO_2, %	50 (40-61)	54 (49-75)[3]	55 (40-65)	49 (41-75)
P_aO_2/F_iO_2	235 (110-302)	164 (140-216)[7]	188 (110-293)	213 (140-302)
Venous admixture, %	26 (9-41)	33 (30-42)[3]	32 (11-49)	27 (9-48)
Plateau pressure, cm H_2O	24 (14-40)	33 (30-42)[6]	29 (18-39)	32 (15-42)
Tidal volume, mL	550 (460-800)	590 (535-680)	580 (460-800)	550 (470-680)
PEEP, cm H_2O	10 (1-22)	16 (13-20)[7]	11 (1-22)	11 (5-20)
Compliance, mL/cm H_2O	41 (24-62)	35 (25-45)[7]	37 (24-62)	36 (25-61)
Number of quadrants	2 (0-4)	2 (1-4)[7]	2 (1-3)	2 (0-4)
Lung injury score	2.0 (0.7-2.5)	3.0 (2.7-3.5)[7]	2.4 (1.5-3.0)	2.3 (0.7-3.5)
Pneumonia	7 (47)	5 (71)	3 (30)	7 (58)
ARDS	na	na	2 (20)	5 (42)
Length of stay, days	10 (1-58)	21 (6-93)	13 (1-51)	11 (6-93)
Mortality	5 (30)	2 (29)	3 (33)	4 (33)

Median (range) or number of patients, where appropriate. Abbreviations: HR = heart rate, MAP = mean arterial pressure, CVP = central venous pressure, GEDVI = global end-diastolic volume index, CI = cardiac index, COP = colloid osmotic pressure, PLI = pulmonary leak index, EVLW = extravascular lung water, ITBV = intrathoracic blood volume, PBV = pulmonary blood volume, P/S_aO_2 = arterial O_2 pressure/saturation, F_iO_2 = inspiratory O_2 fraction, PEEP = positive end-expiratory pressure, ARDS = acute respiratory distress syndrome. Exact P values <0.10 are given: [1]P=0.080, [2]P=0.078, [3]P=0.056, [4]P=0.047, [5]P=0.025, [6]P=0.012, [7]P=not applicable.

Table 3. Sepsis and pulmonary leak index (PLI)

	Sepsis		PLI	
	Pneumonia n=12	Extrapulmonary n=10	<40 n=6	>40 x10^{-3}/min n=16
Hemodynamic				
HR, /min	98 (64-139)	86 (46-130)	80 (46-130)	104 (64-139)[4]
MAP, mm Hg	71 (60-86)	76 (64-95)	80 (71-89)	69 (60-95)[7]
CVP, mm Hg	7 (3-13)	6 (0-16)	5 (3-16)	7 (0-13)
GEDVI, mL/m^2	909 (556-1214)	741 (591-1447)	878 (725-1447)	867 (556-1196)
CI, L/min/m^2	4.5 (2.9-6.6)	3.1 (2.3-5.3)[8]	3.3 (2.3-5.4)	3.6 (2.6-6.6)
COP, mm Hg	16 (10-19)	16 (13-20)	16 (10-19)	16 (12-20)
Dopamine, mg/h	28 (0-56)	24 (0-40)	22 (0-40)	28 (0-56)
Norepinephrine, mg/h	0.5 (0-1.2)	0.2 (0-0.8)	0.05 (0-0.4)	0.1 (0-1.2)
Pulmonary				
PLI, x 10^{-3}/min	55 (35-204)	42 (17-217)	30 (17-39)	58 (45-217)[12]
Most-least affected, %				
PLI > 40 x 10^{-3}/min	11 (92)	5 (50)[5]	na	na
EVLW, mL/kg	9.0 (3.6-33.9)	7.8 (1.9-14.9)	7.8 (1.9-13.1)	8.5 (3.6-33.9)
EVLW >10 mL/kg	6 (50)	3 (33)	2 (33)	7 (44)
EVLW/ITBV	0.29 (0.13-0.91)	0.28 (0.10-0.68)	0.24 (0.10-0.32)	0.32 (0.13-0.91)[2]
EVLW/PBV	15 (0.5-17.3)	1.6 (0.5-19.7)	1.2 (0.5-1.8)	1.9 (0.5-19.2)[2]
P_aO_2, mm Hg	97 (65-141)	112 (82-124)	106 (82-118)	101 (65-141)
S_aO_2, %	97 (93-98)	97 (96-99)[3]	97 (96-99)	97 (93-96)
F_iO_2, %	53 (40-75)	48 (40-61)[3]	46 (40-61)	50 (41-75)
P_aO_2/F_iO_2	183 (110-256)	235 (164-302)[6]	219 (164-293)	197 (110-302)
Venous admixture, %	34 (19-49)	25 (9-33)[11]	24 (9-30)	32 (16-49)[9]
Plateau pressure, cm H_2O	31 (14-42)	30 (16-40)	21 (14-35)	31 (15-42)
Tidal volume, mL	595 (500-800)	550 (460-620)[1]	550 (460-620)	590 (470-800)
PEEP, cm H_2O	12 (1-20)	11 (6-22)	10 (1-22)	12 (5-20)
Compliance, mL/cm H_2O	37 (27-56)	36 (25-62)	42 (35-62)	36 (25-61)
Number of quadrants	3 (2-4)	1 (0-4)[10]	2 (1-4)	2 (0-4)
Lung injury score	2.5 (1.5-3.5)	2.1 (0.7-2.7)	2.1 (1.5-2.7)	2.5 (0.7-3.5)
Pneumonia	na	na	1 (16)	11 (69)[5]
ARDS	5 (42)	2 (20)	1 (16)	6 (37)
Length of stay, days	12 (1-51)	17 (6-93)	10 (6-93)	13 (1-58)
Mortality	5 (42)	2 (20)	0	7 (44)

Median (range) or number of patients, where appropriate. Abbreviations: HR = heart rate, MAP = mean arterial pressure, CVP = central venous pressure, GEDVI = global end-diastolic volume index, CI = cardiac index, COP = colloid osmotic pressure, PLI = pulmonary leak index, EVLW = extravascular lung water, ITBV = intrathoracic blood volume, PBV = pulmonary blood volume, P/S_aO_2 = arterial O_2 pressure/saturation, F_iO_2 = inspiratory O_2 fraction, PEEP = positive end-expiratory pressure, ARDS = acute respiratory distress syndrome. Exact P values <0.10 are given: [1]P=0.095, [2]P=0.085, [3]P=0.069, [4]P=0.059, [5]P=0.056, [6]P=0.05, [7]P=0.040, [8]P=0.025, [9]P=0.017, [10]P=0.014, [11]P=0.003, [12]P=not applicable.

ICU mortality. There was a tendency for a predictive value of PLI, and not of EVLW, for mortality (ROC AUC 0.73, 95% CI 0.51-0.90, P=0.08), since all patients who died (n=7, 32%) had a PLI >40 x 10^{-3}/min only.

DISCUSSION

Our results suggest that, in mechanically ventilated patients with sepsis and ALI/ARDS, increased venous admixture and impaired oxygenation are better explained by a lung vascular injury than by edema, even though a lung vascular injury relates to a rise in EVLW to PBV or ITBV ratio and the latter bears some relation to radiographic pulmonary densities. Moreover, the PLI is more often elevated, venous admixture is higher and radiographic densities are more extensive during pneumonia than during extrapulmonary sepsis, particularly when acquired in the ICU. The data also argue in favour of extensive radiographic pulmonary densities caused by consolidations rather than by edema or atelectasis, during pneumonia.

Absent relations among edema (EVLW), radiographic densities and gas exchange abnormalities in the lungs, may be due to the relatively small number of patients studied. However, other authors have also described absent or poor relations between radiographic pulmonary densities, gas exchange and EVLW (10,12,14), even though basal pulmonary densities on CT scan may directly correlate to venous admixture, attributable to alveolar collapse and/or edema in non-aerated tissue, during acute respiratory failure (6,7). The associations between vascular injury and venous admixture and between radiographic pulmonary densities to EVLW only when normalised for blood volumes (and not to gas exchange/mechanical disturbances) otherwise favour that the greater vascular injury during pneumonia resulted in consolidation rather than edema or alveolar collapse. The absence of any differences among patients with or without evidence for basal atelectasis also argues in favour of consolidations induced by vascular injury, even though plain radiography may underestimate dorsal atelectasis as compared to CT scanning (6,7). In turn, this may partly explain less response of oxygenation during attempts to recruit collapsed alveoli with high ventilatory pressures in pneumonia than in extrapulmonary ALI/ARDS, as suggested before in animal and clinical studies (8,9,24). We did not perform ventilatory recruitment maneuvers in our patients to verify this hypothesis, in the absence of uniformly accepted techniques to compare responses. We also did not perform CT scanning because of the transport involved and the poor differentiation by the

technique between edema, atelectasis and collapse (7).

We nevertheless cannot completely exclude that during pneumonia the edema fluid was less accessible to the thermal indicator than during extrapulmonary sepsis (16,17). Indeed, experimental literature suggests that, as compared to the gravimetric methods, the double indicator dilution method can somewhat underestimate pulmonary edema in direct, as opposed to indirect ALI/ARDS (16,17). That increased permeability was only weakly linked to edema (Fig. 1), may also relate, in part to sampling error by the radionuclide probes, and to the concomitant effect of Starling forces that also affect edema formation in the lungs. In any case, EVLW was normal in about 30% of patients, in exact agreement with the literature, showing that the EVLW may be normal, even during ARDS, thereby again arguing against edema to explain radiographic pulmonary densities (11-13,15).

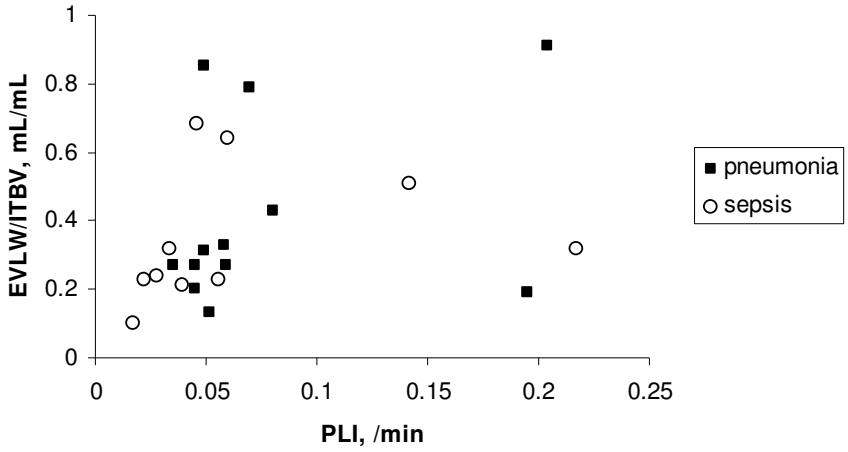

Figure 1. Relation between pulmonary leak index (PLI) and ratio between extravascular lung water (EVLW) and intrathoracic blood volume (ITBV), which is normally 0.2-0.3, in patients with pneumonia or sepsis. r_s=0.46, P=0.032. A similar direct relation was observed for PLI versus EVLW/pulmonary blood volume. Open symbols: extrapulmonary sepsis; closed symbols: pneumonia.

The EVLW to ITBV or PBV ratios have been suggested to reflect increased permeability edema, but this has not yet been validated before (12,18-20), even though we already noted high ratios concomitantly with an elevated PLI after major vascular surgery (19). In contrast, a high ratio may also result from a low plasma colloid osmotic pressure promoting fluid filtration into the lungs, rather than increased

permeability, at least after cardiac surgery (21). Our present study indicates (for the first time) that there is indeed a moderate and direct relation between independently measured pulmonary protein permeability and EVLW ratios, particularly during extrapulmonary sepsis and independently of plasma colloid osmotic pressure.

Conversely, our current data suggest that the PLI is a greater determinant of the manifestations of sepsis-induced lung injury, than the EVLW. In contrast to the EVLW, the PLI was elevated in all patients. Moreover, the PLI had a greater predictive value for outcome than EVLW, which was of prognostic significance in critical illness and ARDS in some but not in other studies (12-14). In a previous study, we reported that patients with pneumonia had an increasing PLI when progressing from ALI to ARDS, and a high PLI at most affected than least affected sides (3). In the current study, we confirm these observations and demonstrate that, venous admixture is greater during pneumonia than during extrapulmonary sepsis, associated with more pulmonary radiographic densities and a higher frequency of an increased PLI. The relation of venous admixture to the PLI indeed suggests that, during pneumonia, the increase in venous admixture was not solely caused by a higher cardiac output. That total respiratory compliance does not differ between ARDS types has been reported before, where direct ARDS (pneumonia) may be associated with low lung compliance and indirect ARDS (extrapulmonary sepsis) with low chest wall compliance (9). We measured total dynamic respiratory compliance and did not separate lung and chest wall contributions. A limitation of the study is the derivation of venous admixture from central venous rather than mixed venous blood. Other investigators, however, have shown that, in spite of some absolute differences when lower body O_2 extraction is lower than in the superior caval vein, changes in central venous track changes in mixed venous hemoglobin saturation (23). In our patients, the oxygenation ratio inversely correlated to venous admixture, suggesting that central venous blood saturation was a major determinant of arterial oxygenation.

In conclusion, our study in mechanically ventilated patients with sepsis-induced ALI/ARDS suggests that a lung vascular injury with consolidation rather than edema or atelectasis, is largely responsible for impaired oxygenation. This may hamper alveolar

recruitment (8,9), may limit the effect of diuretics (25) and calls for anti-inflammatory strategies (26).

REFERENCES

1. Raijmakers PGHM, Groeneveld ABJ, Teule GJJ, Thijs LG. Diagnostic value of the Gallium-67 pulmonary leak index in pulmonary edema. J Nucl Med 1996; 37: 1316-1322
2. Groeneveld ABJ. Radionuclide assessment of pulmonary microvascular permeability. Eur J Nucl Med 1997; 34: 449-461
3. Groeneveld ABJ, Raijmakers PGHM. The ^{67}Ga transferrin pulmonary leak index in pneumonia and associated adult respiratory distress syndrome. Clin Sci 1997; 92: 463-470
4. Groeneveld ABJ, Raijmakers PGHM. The ^{67}gallium-transferrin pulmonary leak index in patients at risk for the acute respiratory distress syndrome. Crit Care Med 1998; 26: 685-691
5. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138: 720-723
6. Gattinoni L, Pesenti A, Bombino M, et al. Relationships between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. Anesth 1988; 69: 824-832
7. Drummond GB. Computed tomography and pulmonary measurements. Br J Anaesth 1998; 80: 665-671
8. Pelosi P, D'Onofrio D, Chiumello D, et al. Pulmonary and extrapulmonary acute respiratory distress syndromes are different. Eur Respir J 2003; 22 (Suppl 42): 48S-56S
9. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med 1998; 158: 3-11
10. Halperin BD, Feley TW, Mihm FG, Chiles C, Guthaner DF, Blank NE. Evaluation of the portable chest roentgenogram for quantitating extravascular lung water in critically ill adults. Chest 1985; 88: 649-652
11. Michard F, Zarka V, Alaya S. Better characterization of acute lung injury/ARDS using lung water. Chest 2004; 125: 1166
12. Martin GS, Eaton S, Mealer M, Moss M. Extravascular lung water in patients with severe sepsis: a prospective cohort study. Crit Care 2005; 9: R74-R82
13. Sakka SG, Klein M, Reinhart K, Meier-Hellman A. Prognostic value of extravascular lung water in critically ill patients. Chest 2002; 122: 2080-2086
14. Davey-Quinn A, Gedney JA, Whiteley SM, Bellamy MC. Extravascular lung water and acute respiratory distress syndrome-oxygenation and outcome. Anaesth Intensive Care 1999; 27: 357-362

15. Groeneveld AB, Polderman KH. Acute lung injury, overhydration or both? Crit Care 2005; 9: 136-137
16. Groeneveld AB, Verheij J. Is pulmonary edema associated with a high extravascular thermal volume? Crit Care Med. 2004; 32: 899-901
17. Roch A, Michelet P, Lambert D, et al. Accuracy of the double indicator method for measurement of extravascular lung water depends on the type of acute lung injury. Crit Care Med 2004; 32: 811-817
18. Honoré PM, Jacquet L.M, Beale RJ, et al. Effects of normothermia versus hypothermia on extravascular lung water and serum cytokines during cardiopulmonary bypass: a randomized, controlled trial. Crit Care Med 2001; 29: 1903-1906
19. Groeneveld ABJ, Verheij J, Van den Berg FG, Wisselink W, Rauwerda JA. Increased pulmonary capillary permeability and extravascular lung water after major vascular surgery: effect on radiography and ventilatory variables. Eur J Anaesthesiol 2006; 23: 36-41
20. Matejovic M, Krouzecky A, Rokyha R, Novak I. Fluid challenge in patients at risk for fluid loading-induced pulmonary edema. Acta Anaesthesiol Scand 2004; 48: 690-673
21. Verheij J, Van Lingen A, Raijmakers PGHM, et al. Pulmonary abnormalities after cardiac surgery are better explained by atelectasis than by increased permeability oedema. Acta Anaesthesiol Scand 2005; 49: 1302-1310
22. Gödje O, Peyerl M, Seebauer T, Dewald O, Reichart B. Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function. Chest 1998; 113: 1070-1077
23. Reinhart K, Bloos F. The value of venous oximetry. Curr Opin Crit Care 2005; 11: 259-263
24. Lim S-C, Adams AB, Simonson DA, et al. Intercomparison of recruitment maneuver efficacy in three models of acute lung injury. Crit Care Med 2004; 32: 2371-2377
25. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005; 33: 1681-1687
26. Groeneveld ABJ. Vascular pharmacology of acute lung injury and acute respiratory distress syndrome. Vasc Pharmacol 2002; 39: 247-256

CHAPTER 5

Fluid responsiveness after cardiac or vascular surgery is greater for colloids than for saline

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ABSTRACT

Objective. To study the effects on volume expansion and myocardial function of colloids or crystalloids in the treatment of hypovolemia after cardiac and major vascular surgery.

Design and setting. A single-center, single-blinded, randomized clinical trial at the intensive care unit of a university hospital.

Patients and methods. Patients with low filling pressures and hypotension after cardiac or major vascular surgery were subjected to a 90-min filling pressure-guided fluid challenge, targeting a central venous pressure (CVP) of 13 mm Hg or a pulmonary capillary wedge pressure (PCWP) of 15 mm Hg, with saline 0.9% (n=16), or the colloid solutions modified fluid gelatin 4% (n=16), hydroxyethyl starch 6% (HES 200/0.5, n=17) or albumin 5% (n=18). Biochemical variables and hemodynamics (transpulmonary thermodilution) were measured.

Results. More saline than colloids was infused (P<0.005). Saline decreased colloid osmotic pressure (COP), while increasing in the other groups (P<0.001). Plasma volume increased less in saline than in the colloid groups. Cardiac index increased by median 13% (ns) in the saline group, and 22% in the colloid groups (P<0.005 between groups). The rise in left ventricular stroke work index was greater in the colloid than in the saline groups. Colloids were equally effective. The rise in cardiac index related to the rise in plasma volume and global end-diastolic volume, confirming plasma volume and preload augmentation by pressure-guided fluid loading.

Conclusion. After cardiac or major vascular surgery, pressure-guided fluid responsiveness is dependent on the type of fluid used. Colloid fluid loading leads to a greater increase in preload-recruitable cardiac and left ventricular stroke work indices than that with saline, because of greater plasma volume expansion following an increase in plasma colloid osmotic pressure.

INTRODUCTION

Hypovolemia is relatively common after major surgery, including cardiac and vascular surgery, and associated with major fluid shifts and hypotension (1,2). Fluid loading is the mainstay of treatment, but the choice among the available fluids is unclear, even though addressed by several studies in cardiac surgery (3-14) or vascular surgery patients (15-20). In any case, (colloid) fluid loading may lead to an increase in cardiac index in surgical patients and may reduce intensive care unit and hospital lengths of stay (2,10,21).

The colloid-crystalloid controversy refers to the ongoing debate on the relative merits and detriments of resuscitation from hypovolemia with infusion of colloid or crystalloid solutions (22-24). This includes the role of plasma colloid osmotic pressure (COP) in retaining fluids intravascularly and in the allegedly greater speed and extent by which colloids, maintaining COP, restore plasma volume and blood flow as opposed to crystalloids, which dilute plasma proteins and lower COP (22-24). Indeed, it is commonly believed, but also doubted, that 2-3 times more crystalloid than colloid fluid is needed to restore and maintain filling pressures in the treatment of hypovolemia, and the ratio of crystalloid to colloid fluid volume to maintain intravascular filling may range from 1 to 5, after cardiac or major vascular surgery (6,8,10,12,14-18,20,24,25). The colloid-crystalloid controversy may also stem in part from the time-dependency of fluid effects and the monitored end point for adequacy of fluid resuscitation used. Filling pressures of the heart may be poor indicators of cardiac preload and fluid responsiveness and global end-diastolic volume assessed from transpulmonary thermodilution, may be superior in that respect (12,26-31). Finally, the colloid-colloid controversy refers to the potential of artificial colloids to replace human protein colloids (3-5,7-11). Indeed, starch infusions may result in better cardiac performance than those of saline or even protein colloids (32), which may have negative inotropic effects via binding of circulating calcium (33). Starches may ameliorate cardiac ischemia/reperfusion injury, at least in animals (34).

For the current study, we hypothesized that colloid fluid loading, by maintaining plasma COP, results in a greater plasma volume expansion and cardiac output elevation with time than that with saline, after cardiac or vascular surgery. We also hypothesized that exogenous colloids would perform similar to albumin in this respect. We thus compared saline with various commonly used colloids and evaluated plasma COP, plasma volume and cardiac performance, using a standard pressure-guided fluid challenge protocol over 90 min (35), verified by transpulmonary thermodilution preload measurements (12,26-31).

Table 1. Fluid challenge protocol

Central venous pressure, mm Hg:		
At start:	≤ 8	200 mL/ 10 min
	< 12	100 mL/ 10 min
	= 12	50 mL/ 10 min
During infusion:	increase > 5	Stop
After 10 min:	increase ≤ 2	Continue
	2 < increase < 5	Wait 10 min
	increase > 5	Stop
After 10 min waiting	increase > 2	Stop
	increase ≤ 2	Repeat
Pulmonary capillary wedge pressure, mm Hg:		
At start	≤ 10	200 mL/ 10 min
	< 14	100 mL/ 10 min
	= 14	50 mL/ 10 min
During infusion	increase > 7	Stop
After 10 min	increase ≤ 3	Continue
	3 < increase < 7	Wait 10 min
	increase > 7	Stop
After 10 min waiting	increase > 3	Stop
	increase ≤ 3	Repeat

Modified from Weil MH, et al. Anesth Analg 1979; 58: 124-132 (ref 35).

PATIENTS AND METHODS

This study is a prospective, stratified, randomized, single-blinded and single-centre clinical trial. The study was approved by the Ethical Committee of the Vrije Universiteit Medical Center and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained in each of the 89 eligible patients, pre-operatively. The hospital pharmacy assigned the patients randomly, via the sealed envelop method, to various

groups, after stratification between cardiac (n=40) or major vascular surgery (n=28). Of the 89, 68 patients fulfilled the study criteria at the arrival at the intensive care unit (ICU) post-operatively. One cardiac patient assigned to saline, however, was excluded because of technical failures and one patient assigned to the gelatin group inadvertedly received albumin. Hence, 67 consecutive patients were included in the study, leaving 16 saline, 16 gelatin, 17 hydroxyethyl starch and 18 albumin-loaded patients.

Table 2. Patient characteristics

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
Age, year	64 (53-75)	63 (41-75)	66 (38-74)	62 (51-74)
Sex, M/F	14/2	16/0[A]	10/7[A]	14/4[A]
APACHE II	8 (3-17)	8 (2-18)	9 (2-14)	9 (3-15)
Cardiac surgery	9	9	10	11
Vascular surgery	7	7	7	7
Type of surgery				
CABG	4	4	6	6
OPCABG	2	2	2	2
AVR	1	0	1	2
CABG + AVR	2	2	0	1
ASD repair	0	1	1	0
AAA	6	7	2	4
TAA	1	0	3	1
MS	0	0	2	2
CPB, min/N	122 (86-188)/8	96 (85-190)/7	111 (40-168)/11	115 (77-198)/10
Aortic clamping time, min/N	95 (43-140)/14	90 (31-175)/14	76 (26-102)/13	70 (49-113)/14
Inotropic support, µg/kg/min/N				
Dopamine	2 (0-17)/10	2 (0-8)/14	0.5 (0-10)/10	2 (0-8)/13
Nitroglycerin	1 (0-5)/11	1 (0-2)/12	1 (0-5)/15	1 (0-2)/12
Fluid input, mL	1800 (1300-1800)[1]	1800 (900-1800)	1400 (750-1800)	1650 (1250-1800)
Diuresis, mL	435 (90-1350)	385 (150-1440)	435 (120-1050)	529 (90-1350)

Median (ranges) or number (N) where appropriate. Abbreviations: HES = hydroxyethyl starch; CABG = coronary artery bypass grafting; OPCABG = off pump coronary artery bypass grafting; AVR = aortic valve replacement; ASD = atrial septal defect; AAA = abdominal aortic aneurysm; TAA = thoracic aortic aneurysm; MS = mesenteric stenosis; CPB = cardiopulmonary bypass; APACHE = acute physiology and chronic health evaluation; [A]$P<0.05$ between colloid groups; [1]$P<0.005$ saline versus colloids.

The inclusion criteria, judged when the patients arrived at the ICU, were presumed hypovolemia, defined as a systolic blood pressure below 110 mm Hg and reduced filling pressures: a pulmonary capillary wedge pressure (PCWP) at or below 10 mm Hg in the presence of a pulmonary artery catheter (n=49) and proper wedging (n=36) or a central venous pressure (CVP) at or below 8 mm Hg (n=31). At actual

enrollment and start of the protocol, PCWP had to be below 13 and CVP below 12 mm Hg. Patients were thus only included if they had or needed, on clinical grounds, arterial and pulmonary artery or central venous catheters. Exclusion criteria were: age >79 years and known anaphylactoid reactions to colloids.

On the day of surgery, anesthesia was induced by sufentanil, pancuronium and midazolam and maintained by a continuous infusion of propofol with supplemental bolus doses of sufentanil. Radial artery, central venous and, if indicated on clinical grounds, pulmonary artery catheters were inserted for hemodynamic measurements and blood sampling. After tracheal intubation, the lungs were volume-controlled ventilated with a tidal volume of 8-10 mL/kg resulting in an end-tidal CO_2 concentration between 4 and 5%, using an O_2-air mixture with an inspiratory O_2 concentration of 40%. A positive end-expiratory pressure (PEEP) of 5 cm H_2O was applied. 31 cardiac surgery patients and 5 major vascular surgery patients underwent surgery with help of a cardiopulmonary bypass (CPB) or a left-left shunt, respectively (Stockert-Sorin S3, Sorin Biomedica, Mirandola, Modena, Italy). The extracorporeal bypass was primed with Ringer's lactate, gelatin 4%, mannitol, sodium bicarbonate, aprotinin and heparin. After systemic heparinization, extracorporeal blood flow was started, provided that the activated clotting time was prolonged. Non-pulsatile flow rate was maintained at 2-3 L/min/ m^2. Cardiac surgery patients were cooled to 32 °C nasopharyngeal temperature. Mean arterial pressure (MAP) was maintained at 50-80 mm Hg and if the MAP declined to less than 50 mm Hg, the blood flow rate was increased and/or vaso-active drugs were given. After aortic cross-clamping, all cardiac surgery patients received crystalloid cardioplegia for myocardial protection (in total, 2000 mL, potassium 16 mmol/L, 4 °C). Patients were weaned from the CPB/left-left shunt, using inotropic support, if necessary.

After termination of bypass, heparin was neutralized using an equivalent dose of protamine sulphate (3 mg/kg or 1 mg/kg). Autologous blood and residual volume from the extracorporeal circuit were infused as first-choice fluid administration. Guided by low systemic and filling pressures, saline or colloids were infused additionally. If the hemoglobin concentration was less than 6 mmol/L, packed red

blood cells concentrates were infused. At the end of the surgery, a 4F introducing sheath (Arrow, Reading, USA) was inserted into the femoral artery, for use in the study protocol, in 33 cardiac and 21 major vascular surgery patients. All peri-operative care was given by physicians unaware of group assignment, independently from the study protocol.

Study protocol. At the arrival of the patients in the intensive care unit, the study protocol was started. The hospital pharmacy allocated the patients, via the sealed envelope method, to the various groups. Demographics were recorded, including the acute physiology and chronic health evaluation (APACHE-II) score and baseline (t=0 min) measurements of hemodynamics were performed and blood samples taken. Pressures were measured with patients in the supine position after calibration and zeroing to atmospheric pressure at midchest level (Tramscope^{R}, Marquette, Wisc., USA). The CVP and PCWP were taken at end-expiration, the latter after balloon inflation. For the reproducible measurement of the cardiac preload indicator global end-diastolic volume (GEDV, n 700-900 mL/m^2), the transpulmonary thermal indicator dilution technique was used (12,26-31). The measurement involves a central venous injection of 15 mL of an ice-cold 5% glucose solution and concomitant registration of the thermal dilution in the femoral artery, with help of a 3F catheter equipped with a thermistor (PV 2024, Pulsion Medical Systems, Munich, Germany), inserted at the end of surgery via a 4F introducing sheath (Arrow, Reading, USA) and connected to a bedside computer (COLD Z-021, Pulsion Medical Systems, Munich, Germany). Thermodilution measurements of GEDV and cardiac output (mL/min) were done in duplicate and averaged values were taken (31). The ratio between stroke volume and GEDV/4 is the global ejection fraction (GEF, n 25-35%), an indicator of systolic cardiac function (27,30). Arterial and pulmonary artery (n=49) or central venous (n=18) blood samples were obtained for determinations of hemoglobin/hematocrit, partial O_2 pressure and the O_2 content (Sysmex SE-9000, Sysmex Corporation, Kobe, Japan, and Rapidlab 865, Bayer Diagnostics, Tarrytown, NY, USA), lactate and albumin levels (Roche/Hitachi 747, Roche Diagnostics Corporation, Indianapolis, USA) and the COP (membrane osmometer, Osmomat 050, Gonotec, Berlin, Germany, molecular mass cut-off at 20 kDa). After baseline measurements (t=0 min), fluids were dosed during 90 min on the basis of the response within predefined pressure limits, as measured by the

pulmonary artery catheter or central venous catheter according to the protocol depicted in Table 1, as described in the literature (35), and targeting at maximum CVP and PCWP values of 13 and 15 mm Hg, respectively. The maximum amount of fluid infused was thus 1800 mL. In some instances, the PA catheter failed to wedge during fluid loading, so that fluid challenge was guided by PCWP in 36 of 49 patients with PA catheters (9 saline group, 6 gelatin group, 9 HES group and 12 albumin group patients) and by CVP in the remaining 31 patients. In the PCWP-guided patients, the CVP was also measured at the time points of the study. Every 30 min, from t=0 to 90 min, cardiac output and GEDV were measured. Blood samples were taken at t=0 and 90 min. Concomitant treatment such as doses of vasoactive and sedative drugs and ventilatory settings was unchanged during fluid loading. The pulmonary effects of this trial have been published elsewhere (36).

Calculations and statistical analysis. The study had 82% power to detect a statistically significant difference (at two-sided $P<0.05$) in a fluid loading-induced increase in CI, the main study parameter, of 10% (standard deviation of 26%), in saline (n=16) and 32% (standard deviation 25%) in the colloid-loaded patients (n=51). Cardiac output was indexed to body surface area (BSA), yielding cardiac index (CI, L/min/m^2). This was also done for GEDV, yielding GEDVI (mL/m^2). Left ventricular stroke work index (LVSWI, gm/m^2) was calculated as stroke volume x (mean arterial pressure-PCWP) x 0.0136/BSA. Stroke volume index (SVI) is stroke volume/BSA. In patients in whom only CVP was available, PCWP was substituted for by CVP, since increases in CVP and PCWP were similar ($r_s=0.61$, $P<0.001$). The relation between LVSWI and GEDVI is denoted as preload-recruitable stroke work. O_2 delivery and consumption were calculated according to standard formulae. We calculated plasma volume changes from (Hb0/Hb90) - ((1-Hct90)/(1-Hct0)), in which Hb is hemoglobin and Hct hematocrit, measured at 0 and 90 min (37). Data are summarized as median and range, except in the figures where means and standard errors of the mean (SEM) are used, for clarity. The X^2 test was used for categorical variables. We tested for changes between t=90 and t=0 in the group as a whole (Wilcoxon signed-rank test). Differences in baseline variables and/or changes between colloid and saline groups were evaluated with the Mann-Whitney U test and the Kruskal-Wallis non-parametric test was used to evaluate differences among the colloid groups. Groups were also

compared in t=90 min values in SVI, CI and LVSWI. The Friedman test was used to evaluate multiple time-dependent changes, available for CVP, PCWP, CI and GEDV, measured at t=0, 30, 60 and 90 minutes. The non-parametric Spearman rank correlation coefficient was used to express relations. A $P<0.05$ was considered statistically significant, but lower levels of statistical significance were also reported.

Table 3. Laboratory data

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
Hemoglobin, mmol/L				
t=0	6.0 (4.2-7.5)	5.8 (4.3-7.7)	6.0 (3.7-8.9)	5.5 (4.4-9.1)
t=90[A]	6.0 (4.7-7.2)[1]	5.1 (4.0-6.4)	5.0 (3.7-7.5)	4.9 (4.3-7.8)
Plasma volume change, %				
t=0-90	3 (-18-24)[1]	20 (-8-49)	21 (-11-50)	15 (2-43)
Albumin, g/ L				
t=0	22 (14-30)	22 (14-27)	22 (12-27)	21 (15-28)
t=90	23 (12-28)	19 (11-25)[C]	17 (9-24)[C]	35 (28-42)[C]
Colloid osmotic pressure, mm Hg				
t=0	16.8 (10.5-20.6)	17.9 (13.3-21.1)	18.1 (13.5-24.9)	18.1 (13.0-23.8)
t=90[A]	15.4 (9.5-22.9)[1]	19.8 (18.3-24.7)	21.7 (17.5-25.5)	21.2 (15.0-25.8)
pH				
t=0	7.40 (7.28-7.47)	7.40 (7.26-7.46)	7.42 (7.32-7.52)	7.40 (7.33-7.46)
t=90[A]	7.36 (7.26-7.46)	7.40 (7.27-7.44)[B]	7.41 (7.30-7.47)[B]	7.39 (7.26-7.46)[B]
Temperature, °C				
t=0	36.3 (34.9-37.1)	35.9 (34.9-36.6)	35.6 (34.5-37.2)	35.6 (35.0-37.1)
t=90[A]	36.4 (34.8-37.3)	36.2 (35.3-37.2)	35.9 (35.1-38.4)	36.0 (35.1-37.9)

Median (range); [A]$P<0.001$ (for change in whole group); [B]$P<0.05$, [C]$P<0.001$ (for changes among colloid groups); [1]$P<0.001$ (for changes in saline versus colloid groups)

RESULTS

Clinical data. Table 2 shows the patient characteristics: there was a slight imbalance in sex distribution among the groups. In the cardiac surgery patients, the number of grafts (median and ranges) were 4 (1-6) in patients receiving saline, 4 (2-6) patients receiving gelatin, 4 (3-7) patients receiving HES and 4 (1-5) patients receiving albumin (ns between groups). During the study protocol, more saline than colloid fluid solution was infused. Patients had an uneventful recovery except for one cardiac surgery patient in the gelatin group, who eventually died from postoperative complications (cerebral infarction), and one vascular surgery patient in the saline

group, who died one day post-operatively from re-bleeding. Both events were judged not to relate to fluid loading.

Laboratory data (Table 3). Baseline values did not differ. There was a slight difference in changes of pH from t=0 till t=90 between colloid groups. The blood hemoglobin/hematocrit decreased in the colloid versus the saline groups, together with the arterial O_2 content (data not shown), indicative of greater hemodilution. Increases in plasma volume were greater in colloid than in saline groups. The albumin content decreased in gelatin and HES groups and increased in the albumin group. The COP decreased in the saline and increased in the colloid groups. The arterial PO_2 ranged between 66 and 220 mm Hg at baseline, but there were no changes or differences between groups, at similar levels of F_iO_2 and PEEP (data not shown).

Hemodynamics (Table 4). Baseline values did not differ. For all patients together MAP, SVI, CI, GEF and LVSWI increased together with increases in CVP, PCWP and GEDVI. Systemic vascular resistance decreased. Within the group as a whole, heart rate remained constant, although between colloid and saline groups the change in heart rate slightly differed. Time-dependent increases in CVP and PCWP from t=0, 30, 60 to 90 min were statistically significant in all groups ($P<0.005$), for GEDVI only in the albumin group ($P<0.001$). Concomitantly with less CVP increase in saline than in colloid groups (Table 4, Fig. 1), CI only increased in the colloid groups versus the saline group. LVSWI increased in all groups ($P<0.05$). The SVI increased from median 38 mL/min/m^2 in the saline group and from 44-46 mL/min/m^2 in the colloid groups (ns) up to 42 mL/min/m^2 in the saline and up to 51-55 mL/min/m^2 in the colloid groups, values being different between the colloids and saline at t=90 ($P<0.01$). Also, the t=90 min CI and LVSWI differed between saline and colloid groups ($P<0.05$, ns among colloid groups). Fig. 1 and 2 show that the increase in filling pressure/volume and CI differed among the groups, with the smallest increase in the saline-loaded group. Fig. 3 shows that the slope of the LVSWI/GEDVI relation did not differ, suggesting similar cardiac function among groups. The slopes of the relations between filling pressures and GEDVI (compliance) did not differ among the groups either (not shown).

Table 4. Hemodynamic data

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
Heart rate, beats/min				
t=0	78 (55-93)	71 (46-98)	68 (55-88)	70 (46-101)
t=90	70 (56-93)[1]	72 (54-86)	70 (57-87)	80 (40-96)
Mean arterial pressure, mm Hg				
t=0	73 (63-102)	72 (52-84)	80 (59-113)	75 (57-107)
t=90[A]	83 (66-109)	83 (56-97)	89 (67-121)	85 (62-118)
CI, L/min/ m^2				
t=0	3.0 (2.1-4.5)	3.1 (2.2-4.8)	2.7 (1.6-4.4)	3.0 (2.4-4.7)
t=90[A]	3.1 (1.8-5.8)[2]	3.9 (3.5-4.8)	3.9 (2.8-6.2)	3.8 (2.6-5.9)
CVP, mm Hg				
t=0	4 (1-12)	4 (0-8)	3 (0-7)	5 (1-9)
t=90[A]	5.5 (2-13)[3]	7.5 (3-11)	7 (4-12)	8 (4-12)
PCWP, mm Hg	n=9	n=6	n=9	n=12
t=0	6 (4-13)	7.5 (3-10)	7 (3-11)	7 (1-10)
t=90[A]	9 (5-15)[1]	11.5 (7-14)	12.5 (9-15)	11 (8-14)
GEDVI, mL/ m^2	n=14	n=10	n=14	n=16
t=0	894 (614-1131)	944 (755-1331)	908 (584-1563)	842 (537-1149)
t=90[A]	896 (650-1230)	1030 (652-2527)	939 (575-1731)	994 (603-1205)
GEF, %				
t=0	18 (11-30)	23 (11-26)	21 (13-27)	19 (14-41)
t=90[A]	19 (13-31)	25 (14-28)	23 (16-31)	22 (17-37)
LVSWI, gm/ m^2				
t=0	37 (27-66)	42 (21-65)	43 (24-97)	39 (30-76)
t=90[A]	40 (24-123)[1]	57 (34-80)	59 (38-83)	54 (28-106)

Median (range); CI = cardiac index; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; LVSWI = left ventricular stroke work index; GEDVI = global end-diastolic volume index; GEF = global ejection fraction; $P<0.001$ (for change in whole group); [1]$P<0.05$, [2]$P<0.005$, [3]$P<0.001$ (for changes in saline versus colloid groups).

Predictors of CI response. Fig. 4 shows the individual relations between changes in plasma volume and GEDVI versus those in CI and similar relations applied for SVI changes. It is shown that colloid fluid loading resulted in greater increases in plasma volume and GEDVI, determining the CI response, than saline fluid loading, except for one outlier in the saline group. In stepwise linear regression analysis, the CI response depended on the type of fluid, irrespective of baseline values of GEDVI, MAP and filling pressures.

O_2 balance (Table 5). Baseline values did not differ. O_2 delivery and consumption increased similarly among groups. Venous oxygen saturation and lactate levels did not change.

DISCUSSION

After elective cardiac or major vascular surgery, 90 min of filling pressure-guided fluid loading with colloid solutions results in a greater preload-recruitable CI and LVSWI than that with saline loading. Greater fluid responsiveness can be explained by a greater plasma volume expanding effect associated with an increase in COP, rather than by changes in cardiac function. Artificial colloids are equally effective as albumin, at least at roughly iso-oncotic concentrations.

Table 5. O_2 balance

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
O_2 delivery, mL/min/m^2				
t=0	486 (215-767)	454 (318-576)	397 (215-556)	415 (299-1044)
t=90[A]	512 (219-984)	505 (342-581)	452 (296-685)	476 (254-1116)
O_2 consumption, mL/min/m^2				
t=0	103 (26-158)	118 (62-192)	113 (78-243)	127 (53-200)
t=90[A]	145 (73-187)	161 (70-268)	137 (59-203)	138 (89-226)
Venous O_2 saturation				
t=0	0.75 (0.65-0.95)	0.73 (0.63-0.90)	0.75 (0.57-0.83)	0.73 (0.47-0.86)
t=90	0.73 (0.68-0.88)	0.73 (0.60-0.83)	0.78 (0.65-0.87)	0.75 (0.51-0.86)
Lactate, mmol/L				
t=0	1.4 (0.6-4.1)	1.2 (0.7-2.6)	1.1 (0.5-3.4)	1.1 (0.5-3.0)
t=90	1.4 (0.7-4.1)	1.2 (0.7-3.4)	1.2 (0.5-2.9)	1.0 (0.5-2.9)

Median (range); [A]P<0.001 (for change in whole group)

Our study carries the advantage of comparing multiple, common types of resuscitation fluids in standardized fluid challenge protocol, which has not been done in prior studies on cardiac or vascular surgery, either utilizing fixed volume boluses or prolonged (>8 h to days) filling pressure-guided fluid resuscitation (3-20). Moreover, the number of fluids or patients included in earlier studies was generally lower than in ours (3-20). Prior to fluid challenge, our patients had evidence for hypovolemia, e.g. relatively low CVP and PCWP, which, otherwise, may overestimate true filling pressures in the presence of positive airway pressure at the end of expiration. Moreover, most patients were dependent on vasopressors. The baseline GEDVI may have been normal, but may still be associated with hypovolemia and preload recruitability in patients with cardiac dysfunction and the need for dilatation to

maintain CI, described after cardiac surgery (26-29,31).

The hemodiluting and plasma volume expanding effects of colloids were greater than those of saline, even though the total amount of fluids used was somewhat greater for saline. That saline loading somewhat decreased heart rate as compared to colloids can be attributed to the greater volume, at room temperature, passing the heart during infusion, since relatively cold infusion fluids may have a negative chronotropic effect.

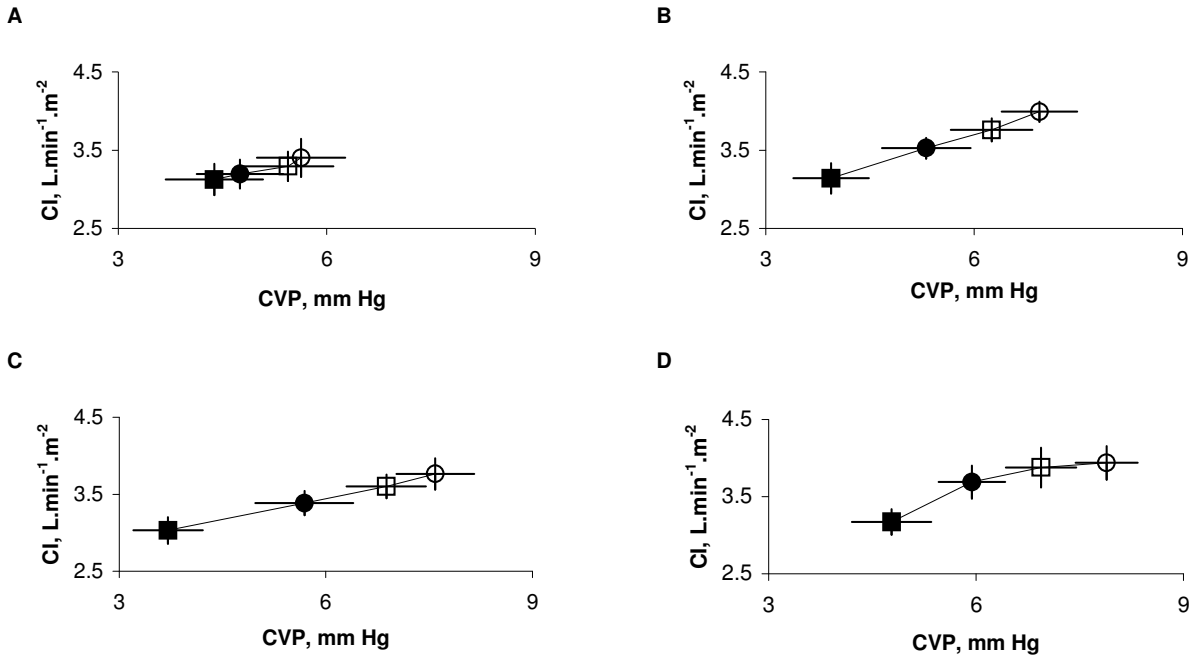

Figure 1. Mean ± SEM for cardiac index (CI) versus filling pressure (CVP, central venous pressure) in the various groups (Panel A: saline; panel B: gelatin; panel C: hydroxyethyl starch; panel D: albumin), at the 4 time points of fluid loading (t=0 ■, t=30 ●, t=60 □, and t=90 ○ min). Baseline CI did not differ and increases were only statistically significant in gelatin, hydroxyethyl starch and albumin groups (P<0.001).

The similar slopes of preload-recruitable CI and LVSWI support similar cardiac systolic function among the fluid groups (30). The GEDVI measurements also confirmed the filling pressure responses (Fig. 2). These measurements were included since fluid-filled catheter-derived filling pressures have traditionally been used and are still widely employed as indicators of cardiac preload and fluid responsiveness, while filling pressures may be inferior to filling volumes in this respect (12,26-31). The difference in fluid responsiveness between crystalloid and colloid fluids can thus be attributed to differences in cardiac filling rather than in

cardiac function. The lack of saline loading to increase CI and LVSWI can be easily explained by saline extravasating in the course of time during the fluid challenge upon transient increases in filling pressures.

Our results confirm the hitherto controversial view that colloid solutions are better retained intravascularly because of their colloid osmotic properties and therefore result in greater and faster plasma volume expansion and fluid responsiveness of CI and LVSWI than saline. Indeed, there is one recent study showing that the intravascular retention of albumin is greater than that of saline after cardiac surgery, as inferred from measurements of plasma and extravascular fluid volumes (14).

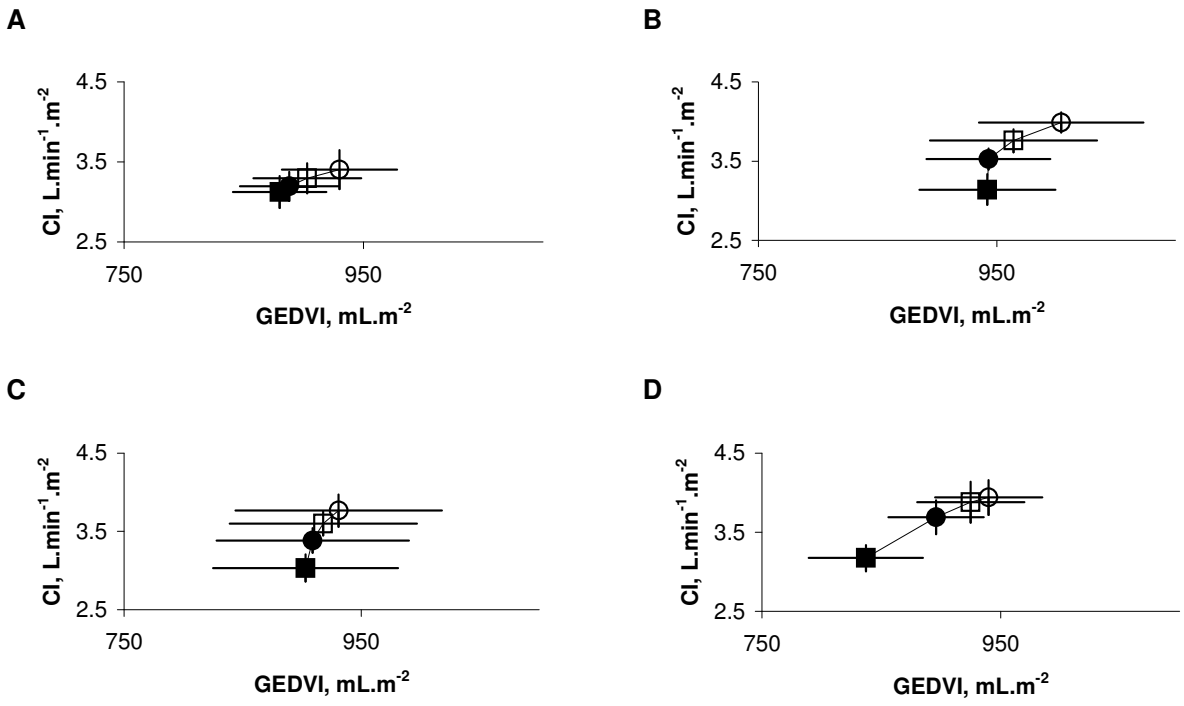

Figure 2. Mean ± SEM for cardiac index (CI) versus global end-diastolic volume index (GEDVI) in the various groups (Panel A: saline; panel B: gelatin; panel C: hydroxyethyl starch; panel D: albumin), at the 4 time points of fluid loading (t=0 ■, t=30 ●, t=60 □, and t=90 ○ min). Baseline values and slopes did not differ.

A study comparing dextran and saline in vascular surgery patients demonstrated the importance of a colloid solution to maintain the intravascular volume, measured with radiolabeled albumin (19). Our study confirms earlier trials comparing crystalloid with colloid fluid resuscitation after cardiac surgery and vascular surgery suggesting that more crystalloid than gelatin, starch or dextran is needed to maintain cardiac output

(8,10,12,15,17,20). Our study contrasts with studies showing similar volumes and hemodynamic effects of crystalloids and colloids after surgery (6) and the recent SAFE study on albumin 4% versus saline fluid resuscitation in intensive care unit patients, showing only minimally greater intravascular volume expanding effects of albumin at only slightly greater saline requirements (25). However, cardiac surgery patients were excluded in this study and there was no rigid fluid challenge protocol with hemodynamic monitoring, potentially masking differences in fluid properties and hemodynamic actions.

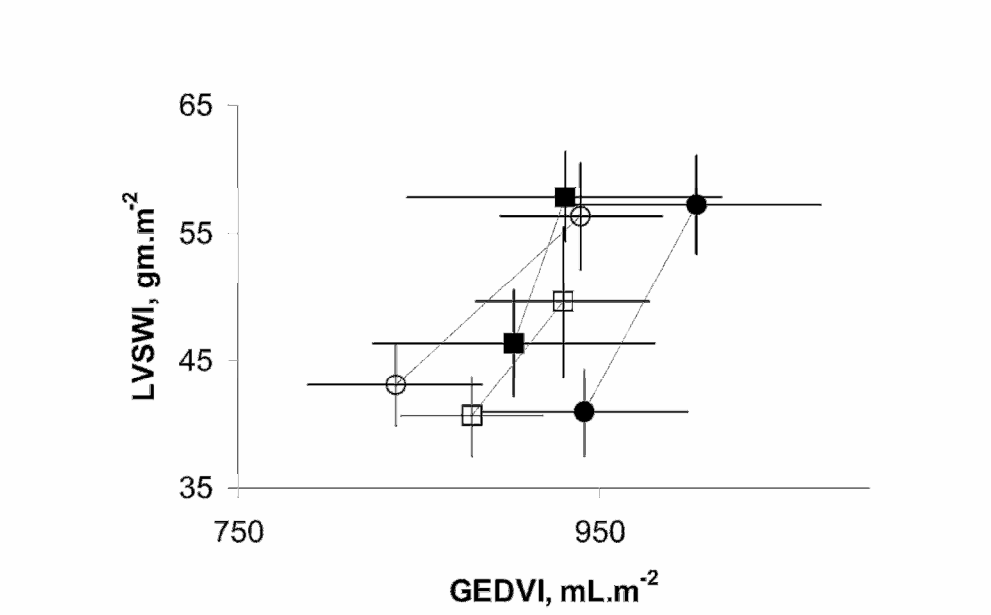

Figure 3. Mean ± SEM for preload-recruitable stroke work (LVSWI, left ventricular stroke work) in saline (□), gelatin (●), hydroxyethyl starch (■) and albumin (○) -loaded patients with global end-diastolic volume index (GEDVI) on the x-axis (from t=0 to 90 min only). Baseline values and slopes did not differ among groups, while the LVSWI attained differed (P=0.021) between saline and colloid groups.

It has been suggested that the heart during and after cardiac surgery is susceptible for myocardial edema and for postischemic systolic and diastolic dysfunction (38). Colloid solutions used to prime the cardiopulmonary bypass system could ameliorate such effect (38,39) and postoperative administration of hyperoncotic albumin may thus have a positive inotropic effect, as compared to saline (13). On the other hand, the rise in CI with albumin appeared less than with saline at similar filling pressures in a study in vascular surgery patients (16), and this difference can be explained by either

insufficient preload or perhaps by the negative inotropic effect of calcium binding by albumin (33), which was otherwise not evident in our study. By measuring filling volumes in addition to filling pressures, changes in myocardial diastolic and systolic function could be assessed in our study (12,26-31). There was no change in the slope of the filling pressure to GEDVI relation, suggesting no differences in myocardial compliance and therefore in myocardial edema among the groups, even though COP was higher in colloid-loaded patients. Hence, our results do not indicate, at least after cardiac surgery in man, that starch ameliorates ischemia/reperfusion injury of the heart and resultant myocardial edema, as in animal models of myocardial injury (34). In our study, there was no clear hemodynamic difference among the colloid solutions, so that non-protein colloid solutions could substitute for protein-based solutions, at least in the acute treatment of hypovolemia, thereby agreeing with some studies (3,4,5). This does not confirm some other trials, suggesting hemodynamic inferiority of protein versus non-protein colloid fluids (7,9,11,32). The differences may partly relate to imprecise hemodynamic monitoring, rather than on major differences in hemodynamic actions of iso-oncotic colloid fluids, even though the number of patients in our study, adequately powered to detect CI differences among saline and colloid fluids, may have been insufficient to find small differences among the latter.

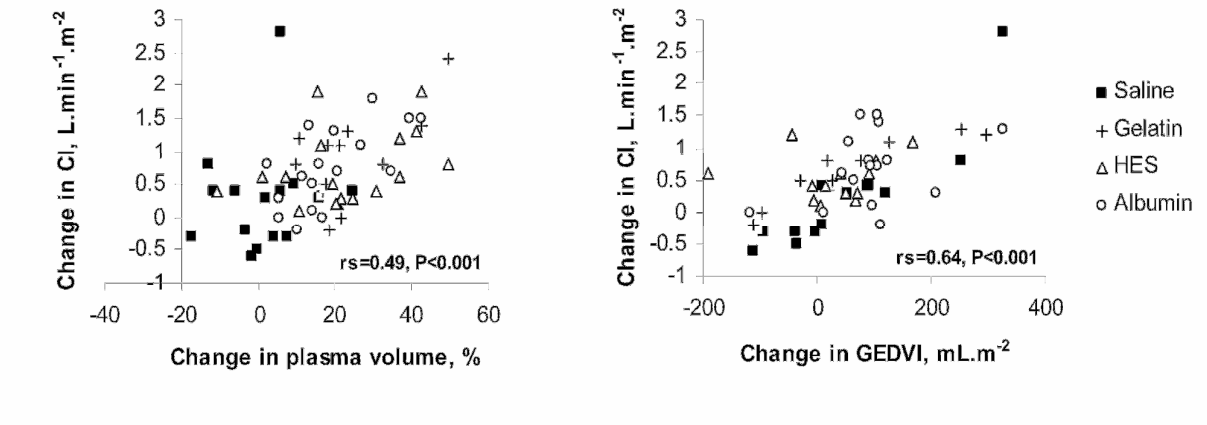

Figure 4. Changes in cardiac index (CI) versus changes in plasma volume (left panel) and global end-diastolic volume index (GEDVI) (right panel): r_s=0.49, P<0.001 and r_s=0.64, P<0.001, respectively. It is shown that saline loading increased PV, GEDVI and thus CI less than colloid loading.

Both DO_2 and VO_2 increased in our patients during fluid loading, in the presence of normal lactate levels. Together with the postoperative rise in temperature, this suggests that the increase in VO_2 and thus in DO_2 was caused by a rise in O_2 demand rather than by VO_2 supply-dependency (40). Some caution is warranted, however, as the ranges of DO_2 changes may have been insufficient to rule out mathematical coupling and a spurious relation between DO_2 and VO_2 (40). The drawback of expansion of plasma volume is hemodilution (14), so that O_2 delivery increases did not differ among fluid types. In any case, the increase in CI measured at 90 min after completion of the protocol was still greater in colloid than in saline-loaded patients (P=0.01, data not shown) and such sustained effects in CI have been associated with shorter durations of stay of major surgery patients (2,10,21).

In conclusion, our study suggests that, during 90 min of pressure-guided fluid loading to augment preload, fluid responsiveness is greater with colloid than saline fluids in presumably hypovolemic patients after cardiac or major vascular surgery. This supports the idea that the plasma COP is operative clinically, independently of blood albumin concentrations, in retaining fluids intravascularly.

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REFERENCES

1. Boldt J. Volume replacement in the surgical patient - does the type of solution make a difference? Br J Anaesth 2000; 84: 783-793
2. Gan TJ, Soppitt A, Maroof M, El-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PSA. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97: 820-826

3. Diehl JT, Lester JL, Corgrove DM. Clinical comparison of hetastarch and albumin in postoperative cardiac patients. Ann Thorac Surg 1982; 34: 674-677
4. Moggio RA, Chan Rha C, Somberg ED, Praeger PI, Pooley RW, Reed GE. Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. Crit Care Med 1983; 11: 943-945
5. Kirklin JK, Lell WA, Kouchoukos NT. Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. Ann Thorac Surg 1984; 37: 40-46
6. Gallagher JD, Moore RA, Kerns D, Jose AB, Botros SB, Flicker S, Naidech H, Clark DL. Effects of colloid or crystalloid administration on pulmonary extravascular lung water in the postoperative period after coronary artery bypass grafting. Anesth Analg 1985; 64: 753-758
7. Karanko MS. Effects of three colloid solutions on plasma volume and hemodynamics after coronary bypass surgery. Crit Care Med 1987; 15: 1015-1022
8. Karanko MS, Klossner JA, Laaksonen VO. Restoration of volume by crystalloid versus colloid after coronary artery bypass: hemodynamics, lung water, oxygenation, and outcome. Crit Care Med 1987; 15: 559-566
9. London MJ, Ho JS, Triedman JK, Verrier ED, Levin J, Merrick SH, Hanley FL, Browner WS, Mangano DT. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg 1989; 97: 785-797
10. Ley SJ, Miller K, Skow P, Preisig P. Crystalloid versus colloid fluid therapy after cardiac surgery. Heart Lung 1990; 19: 31-40
11. Mastroianni L, Low HBC, Rollman J, Wagle M, Bleske B, Chow MSS. A comparison of 10% pentastarch and 5% albumin in patients undergoing open-heart surgery. J Clin Pharmacol 1994; 34: 34-40
12. Wahba A, Sendtner E, Strotzer M, Birnbaum DE. Fluid therapy with Ringer's solution versus Haemaccel following coronary artery bypass surgery. Acta Anaesthesiol Scand 1996; 40: 1227-1233
13. Magder S, Lagonidis D. Effectiveness of albumin versus normal saline as a test of volume responsiveness in post-cardiac surgery patients. J Crit Care 1999; 14: 164-171
14. Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in cardiac surgical patients. Crit Care Med 2001; 29: 2299-2302
15. Virgilio RW, Rice CL, Smith DE, James DR, Zarins CK, Hobelmann CF, Peters RM. Crystalloid vs. Colloid resuscitation: Is one better? Surg 1979; 85: 129-139
16. Boutros AR, Ruess R, Olson L, Hoyt JL, Baker WH. Comparison of hemodynamic, pulmonary, and renal effects of use of three types of fluid after major surgical procedures on the abdominal aorta. Crit Care Med 1979; 7: 9-13

17. Zetterström H. Albumin treatment following major surgery. II. Effects on postoperative lung function and circulatory adaptation. Acta Anaesth Scand 1981; 25: 133-141
18. Shires GT, Peitzman AB, Albert SA, Illner H, Silane MF, Perry MO, Shires GT. Response of extravascular lung water to intraoperative fluids. Ann Surg 1983; 197: 515-519
19. Dawidson IJA, Willms CD, Sandor ZF, Coorpender LL, Reisch JS, Fry WJ. Ringer's lactate with or without 3% dextran-60 as volume expander during abdominal aortic surgery. Crit Care Med 1991; 19: 36-42
20. Marik PE, Iglesias J, Maini B. Gastric intramucosal pH changes after volume replacement with hydroxyethyl starch or crystalloid in patients undergoing elective abdominal aortic aneurysm repair. J Crit Care 1997; 12: 51-55
21. McKendry M, McGloin H, Saberi D, Caudwell L, Brady AR, Singer M. Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. Br Med J 2004; 329: 258-261
22. Schierhout G, Robert I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. Br Med J 1998; 316: 961-964
23. Choi PT-L, Yip G, Quinonez L, Cook D. Crystalloids versus colloids in fluid resuscitation: a systematic review. Crit Care Med 1999; 27: 200-210
24. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2004
25. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350: 2247-2256
26. Gödje O, Peyerl M, Seebauer T, Lamm P, Mair H, Reichart B. Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volume as preload indicators in cardiac surgery patients. Eur J Cardiothorac Surg 1998; 13: 533-540
27. Gödje O, Peyerl M, Seebauer T, Dewald O, Reichart B. Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water and liver function. Chest 1998; 113: 1070-1077
28. Hinder F, Poelaert JI, Schmidt C, Hoeft A, Möllhoff T, Loick HM, Van Aken H. Assessment of cardiovascular volume status by transoesophageal echocardiography and dye dilution during cardiac surgery. Eur J Anaesthesiol 1998; 15: 633-640
29. Reuter DA, Felbinger TW, Moerstedt K, Weis F, Schmidt C, Kilger E, Goetz AE. Intrathoracic blood volume index measured by thermodilution for preload monitoring after cardiac surgery. J Cardiothorac Vasc Anesth 2002; 16: 191-196
30. Combes A, Berneau J-B, Luyt C-E, Trouillet J-L. Estimation of left ventricular systolic function by single transpulmonary thermodilution. Intensive Care Med 2004; 30: 1377-1383
31. Groeneveld ABJ, Breukers RMBGE, Verheij J. Clinical value of intrathoracic volumes from transpulmonary dilution. In: Pinsky MR, Payen D, eds. Functional hemodynamic monitoring. Springer Verlag, Berlin 2004, pp 153-165

32. Boldt J, Heesen M, Müller M, Pabsdorf M, Hempelmann G. The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. Anest Analg 1996; 83: 254-261
33. Dahn MS, Ledgerwood AM, Higgins RF. Negative inotropic effect of albumin resuscitation for shock. Surgery 1979; 86: 235-240
34. Zikria BA, Subbarao C, Oz MC, Popilkis SJ, Sachdev R, Chauban P, Freeman HP, King TC. Hydroxyethyl starch macromolecules reduce myocardial reperfusion injury. Arch Surg 1990; 125: 930-934
35. Weil MH, Henning RJ. New concepts in the diagnosis and fluid treatment of circulatory shock. Thirteenth annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture. Anesth Analg 1979; 58: 124-132
36. Verheij J, van Lingen A, Raijmakers PGHM, Rijnsburger ER, Veerman DP, Wisselink W, Girbes ARJ and Groeneveld ABJ. Effect of fluid loading with saline or colloids on pulmonary permeability, oedema and lung injury score after cardiac and major vascular surgery. Br J Anaesth 2005; 96: 21-30
37. Johansen LB, Bie P, Warberg J, Christensen NJ, Hammerum M, Videbaek R, Norsk P. Hemodilution, central blood volume, and renal responses after an isotonic saline infusion in humans. Am J Physiol 1997; 272: R549-R556
38. Geissler HJ, Allen SJ. Myocardial fluid balance: pathophysiology and clinical applications. Thorac Cardiovasc Surg 1998; 46: 242-247
39. Eising GP, Niemeyer M, Günther Th, Tassani P, Pfauder M, Schad H, Lange R. Does a hyperoncotic cardiopulmonary bypass prime affect extravascular lung water and cardiopulmonary function in patients undergoing coronary artery bypass surgery? Eur J Cardiothorac Surg 2001; 20: 282-289
40. Squara P. Matching total body oxygen consumption and delivery: a crucial objective. Intensive Care Med 2004; 30: 2170-2179

CHAPTER 6

Effect of fluid loading with saline or colloids on pulmonary permeability, edema and lung injury score after cardiac and major vascular surgery

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ABSTRACT

Background. The optimal type of fluid for treating hypovolemia without evoking pulmonary edema is still unclear, particularly in the presence of pulmonary vascular injury, as may occur after cardiac and major vascular surgery.

Methods. In a single-centre, prospective, single-blinded clinical trial 67 mechanically ventilated patients were randomly assigned to receive saline, gelatin 4%, HES 6% or albumin 5%, according to a 90 min fluid loading protocol with target central venous pressure of 13 mm Hg and pulmonary capillary wedge pressure of 15 mm Hg, within three hours after cardiac or major vascular surgery. Before and after the protocol, we recorded hemodynamics and ventilatory variables and took chest radiographs. The pulmonary vascular injury was evaluated with help of the ^{67}Ga-transferrin pulmonary leak index (PLI) and extravascular lung water (EVLW). Plasma colloid osmotic pressure (COP) was determined and the lung injury score (LIS) was calculated.

Results. More saline was infused than colloid solutions ($P<0.005$). The COP increased in the colloid groups and decreased in patients receiving saline. Cardiac output rose more in the colloid groups. At baseline, PLI and EVLW were above normal in 60% and 30% of the patients, with no changes after fluid loading, except for a greater PLI decrease in HES than in gelatin-loaded patients. The oxygenation ratio improved in all groups. In the colloid groups, the LIS increased, because of a decrease in total respiratory compliance, probably associated with a rise in intrathoracic plasma volume.

Conclusions. Provided that fluid overloading is prevented, the type of fluid used for volume loading does not effect pulmonary permeability and edema, in patients with acute lung injury after cardiac or major vascular surgery, except for HES that may ameliorate increased permeability. During fluid loading, changes in LIS (and respiratory compliance) do not represent changes in permeability-edema.

INTRODUCTION

Hypovolemia is common in the critically ill and various infusion fluids are available for treatment (1). These include crystalloid and colloid fluids, which, in theory, promote and limit fluid extravasation in the lungs and formation of pulmonary edema, respectively, since the former lower and the latter maintain or even increase plasma colloid osmotic pressure (COP). The so called colloid-crystalloid controversy includes the relative propensity of fluid types to evoke pulmonary edema, which is not yet settled in the absence of direct permeability and edema measurements in most studies (1). Indeed, the controversy is complicated by the idea that the potentially protective role of COP may diminish when permeability is increased, while the propensity for edema formation may increase, unless hydrostatic pressure is kept low, as demonstrated in experimental and human studies (2-4). In the recent SAFE study, resuscitation of critically ill (non-cardiac surgery) patients with albumin or saline proved almost equally safe without differing mortality rates, although pulmonary edema was not studied specifically (5).

Cardiac and major vascular surgery are often complicated by hypovolemic hypotension, necessitating fluid therapy, but the optimal type of fluid for this purpose is hotly debated (1,6-13). Cardiac and major vascular surgery, involving ischemia and reperfusion, are well known risk factors for a systemic inflammatory response and for acute lung injury/acute respiratory distress syndrome (ALI/ARDS), associated with increased capillary permeability in the lungs in some patients, as measured by a non-invasive double radionuclide technique to detect pulmonary ^{67}Ga-transferrin extravasation (14-18). This could thus affect the contribution of infusion fluids to pulmonary edema formation. Indeed, studies documented a rise in extravascular lung water (EVLW) after cardiac or major vascular surgery and fluid loading, at least transiently in some patients (9-11,19-22).

Finally, experimental studies suggest that middle and large molecular solutions of starches may ‘plug’ the leaks during increased permeability after ischemia/ reperfusion, endotoxemia, toxic injury or extracorporeal bypass (23-27). They may

even improve pulmonary dysfunction after aortic surgery in humans (28). Moreover, albumin solutions may have an anti-inflammatory antioxidant effect, thereby ameliorating endothelium-neutrophil interactions in the lungs and increased permeability in experimental studies (29). Infusion fluids may thus affect capillary permeability in the human lungs.

We hypothesized that colloid fluid loading would less aggravate edema formation in the lungs than saline loading, in the treatment of presumed hypovolemia after major surgery, even if complicated by increased pulmonary permeability. We also hypothesized that hydroxyethyl starch or albumin loading would lower increased permeability edema, as compared to gelatin loading. We therefore compared filling pressure-guided fluid challenges (30) with saline and with the colloids gelatin, hydroxyethyl starch (HES) and albumin in their effects on pulmonary capillary permeability, EVLW, COP, and the lung injury score in 67 presumably hypovolemic patients after cardiac or major vascular surgery.

PATIENTS AND METHODS

This study is a prospective, stratified, randomized, single-blinded and single-centre clinical trial. The study was approved by the Ethical Committee of the Vrije Universiteit Medical Center. Written informed consent was obtained in each of the 89 eligible patients, on the day prior to scheduled surgery. The hospital pharmacy assigned the patients randomly, via the sealed envelop method, to various groups, after stratification between cardiac (n=40) or major vascular surgery (n=28). Of the 89, 68 patients fulfilled the study criteria at the arrival at the intensive care unit (ICU) post-operatively. One cardiac patient assigned to saline, however, was excluded because of technical failures and one patient assigned to the gelatin group inadvertedly received albumin. Hence, 67 consecutive patients were included in the study. The inclusion criteria, judged when the patients arrived at the ICU, were presumed hypovolemia, defined as a systolic blood pressure below 110 mm Hg and reduced filling pressures: a pulmonary capillary wedge pressure (PCWP) at or below 10 mm Hg in the presence of a pulmonary artery catheter (n=49) and proper wedging

(n=36) or a central venous pressure (CVP) at or below 8 mm Hg (n=31). Patients were thus only included if they had or needed, on clinical grounds, arterial and pulmonary artery or central venous catheters. Exclusion criteria were: age >79 years and known anaphylactoid reactions to colloids or iodide. On the day of surgery, anesthesia was induced by sufentanil, pancuronium and midazolam and maintained by a continuous infusion of propofol with supplemental bolus doses of sufentanil. Radial artery, central venous and, if indicated on clinical grounds, pulmonary artery catheters were inserted for hemodynamic measurements and blood sampling. After tracheal intubation, the lungs were volume-controlled ventilated with a tidal volume of 8-10 mL/kg resulting in an end-tidal CO_2 concentration between 4 and 5%, using an O_2-air mixture with an inspiratory O_2 concentration of 40%. A positive end-expiratory pressure (PEEP) of 5 cm H_2O was applied. Cardiac surgery patients received 50-100 mg dexamethasone at induction. Thirty-one cardiac surgery patients and 5 major vascular surgery patients underwent surgery with help of a cardiopulmonary bypass (CPB) or a left-left shunt, respectively (Stockert-Sorin S3, Sorin Biomedica, Mirandola, Modena, Italy). The extracorporeal bypass was primed with Ringer's lactate, gelatin 4%, mannitol, sodium bicarbonate, aprotinin and heparin.

After systemic heparinization, extracorporeal blood flow was started, provided that the activated clotting time was prolonged. Non-pulsatile flow rate was maintained at 2-3 L/min/m^2. Cardiac surgery patients were cooled to 32 °C nasopharyngeal temperature. Mean arterial pressure (MAP) was maintained at 50-80 mm Hg and if the MAP declined to less than 50 mm Hg, the blood flow rate was increased and/or vaso-active drugs were given. After aortic cross-clamping, all cardiac surgery patients received crystalloid cardioplegia for myocardial protection (in total, 2000 mL, potassium 16 mmol/L, 4 °C). Patients were weaned from the CPB/left-left shunt, using inotropic support, if necessary and heparin was neutralized using an equivalent dose of protamine sulphate (3 mg/kg or 1 mg/kg). Autologous blood and residual volume from the extracorporeal circuit were infused as first-choice fluid administration. Guided by low systemic and filling pressures, saline or colloids were infused additionally. If the hemoglobin concentration was less than 6 mmol/L, packed red blood cells concentrates were infused. Pre-operative use of aspirin, excessive

bleeding and a long pump-time prompted for administration of donor platelets. At the end of the surgery, a 4F introducing sheath (Arrow, Reading, USA) was inserted into the femoral artery, for use in the study protocol, in 33 cardiac and 21 major vascular surgery patients.

Table 1. Patient characteristics

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
Age, year	64 (53-75)	63 (41-75)	66 (38-74)	62 (51-74)
Sex, M/F	14/2	16/0[a]	10/7[a]	14/4[a]
APACHE II	8 (3-17)	8 (2-18)	9 (2-14)	9 (3-15)
Cardiac surgery	9	9	10	11
Major vascular surgery	7	7	7	7
Type of surgery				
CABG	4	4	6	6
OPCABG	2	2	2	2
AVR	1	0	1	2
CABG + AVR	2	2	0	1
ASD repair	0	1	1	0
AAA	6	7	2	4
TAA	1	0	3	1
MS	0	0	2	2
CPB, min/N	122 (86-188)/8	96 (85-190)/7	111 (40-168)/11	115 (77-198)/10
Aortic clamping time, min/N	95 (43-140)/14	90 (31-175)/14	76 (26-102)/13	70 (49-113)/14
Inotropic support, µg/kg/min/N				
Dopamine	2 (0-17)/10	2 (0-8)/14	0.5 (0-10)/10	2 (0-8)/13
Nitroglycerin	1 (0-5)/11	1 (0-2)/12	1 (0-5)/15	1 (0-2)/12
Fluid infused, mL	1800 (1300-1800)[b]	1800 (900-1800)	1400 (750-1800)	1650 (1250-1800)
Diuresis, mL	435 (90-1350)	385 (150-1440)	435 (120-1050)	529 (90-1350)

Median (ranges) or number (N) where appropriate. Abbreviations: HES = hydroxyethyl starch; APACHE = acute physiology and chronic health evaluation; CABG = coronary artery bypass grafting; OPCABG = off pump coronary artery bypass grafting; AVR = aortic valve replacement; ASD = atrial septal defect; AAA = abdominal aortic aneurysm; TAA = thoracic aortic aneurysm; MS = mesenteric stenosis; CPB = cardiopulmonary bypass; [a]$P<0.05$ between colloid groups, [b] $P<0.005$ saline versus colloids.

Measurements. For the measurement of the pulmonary leak index (PLI), as done in previous studies (14-16), autologous red blood cells were labeled with ^{99m}Technetium (Tc, 11 MBq, physical half-life 6h; Mallinckrodt Diagnostica, Petten, The Netherlands) Transferrin was labeled in vivo, following i.v. injection of ^{67}Gallium (Ga)-citrate, 4.5 MBq for the pre-infusion study and 9 MBq for the post-infusion study (physical half-life 78 h; Mallinckrodt Diagnostica, Petten, The Netherlands). Patients were in the supine position and two scintillation detection probes (Eurorad C.T.T.,

Strasburg, France) were positioned over the right and left lung apices. Starting at the time of the i.v. injection of ^{67}Ga, radioactivity was detected during 30 minutes. The ^{99m}Tc and ^{67}Ga counts were corrected for background radioactivity, physical half-life, spill-over of ^{67}Ga into the ^{99m}Tc window, obtained by in vitro measurement of ^{67}Ga, and expressed as counts per minute (CPM) per lung field. At 1, 5, 8, 12, 16, 20, 25 and 30 minutes after ^{67}Ga injection, blood samples (2 mL aliquots) were taken. Each blood sample was weighed and radioactivity was determined with a single well well-counter (LKB Wallac 1480 WIZARD, Perkin Elmer, Life Science, Zaventem, Belgium), taking background, spillover of ^{67}Ga into ^{99m}Tc and decay into account. Results were expressed as CPM/g. For each blood sample, a time-matched CPM over each lung was taken. A radioactivity ratio was calculated, ($^{67}Ga_{lung}$/$^{99m}Tc_{lung}$)/($^{67}Ga_{blood}$/$^{99m}Tc_{blood}$), and plotted against time. The PLI was calculated from the slope of increase of the radioactivity ratio divided by the intercept, to correct for physical factors in radioactivity detection. The PLI represents the transport rate of ^{67}Ga-transferrin from the intravascular to the extravascular space of the lungs and is therefore a measure of pulmonary vascular permeability. The values for both lung fields were averaged. The upper limit normal for the PLI is 14.7 x 10^{-3}/min and the measurement error is about 10% (14,16).

For the measurement of cardiac output (CO), intrathoracic blood volume (ITBV) and extravascular lung water (EVLW), the transpulmonary thermal-dye dilution technique was used (22,31). This involves a central venous injection of a dye and thermal bolus, 15 mL of 1 mg/mL indocyanine green (ICG) in a ice-cold dextrose 5% solution and concomitant registration of the dye dilution and thermal shift in the femoral artery, with help of the 3F catheter equipped with a thermistor and fiberoptic (PV 2024, Pulsion Medical Systems, Munich, Germany) connected to a bedside computer (COLD Z-021, Pulsion Medical Systems, Munich, Germany). The catheter was introduced via the introducing sheath. Measurements were done in duplicate, irrespective of the ventilatory cycle, and average values were taken. The technique yields the transpulmonary thermodilution CO, and a transit time of the dye in the thorax and thereby the ITBV. From the differences in transit time of the thermal and dye signal, the EVLW is computed (31). The upper limit of normal for the EVLW is 7

mL/kg and the measurement error is about 10%. In overt pulmonary edema, the EVLW is usually doubled. In the absence of a thermal-dye dilution femoral artery catheter, CO was measured by thermodilution via the pulmonary artery catheter since this is almost interchangeable with transpulmonary measurements (31,32). We calculated plasma volume changes from (Hb0/Hb90) - ((1-Hct90)/(1-Hct0)), in which Hb is hemoglobin and Hct hematocrit, measured at 0 and 90 min (33).

Protocol. After surgery, the patients were admitted to the ICU, and connected to the ventilator (Evita 3, Dräger, Lübeck, Germany) and volume-controlled ventilation was started with similar settings as during surgery. The study protocol was started within three hours after arrival. Demographics were recorded, including variables to the acute physiology and chronic health evaluation (APACHE-II) score and baseline measurements of the ^{67}Ga-transferrin PLI (t=-30 to t=0 min) and hemodynamics were performed and an anteroposterior chest radiograph was taken. Pulmonary and systemic hemodynamic variables were measured after calibration and zeroing to atmospheric pressure at mid-chest level (Tramscope^{R}, Marquette, Wisc., USA). Mean pulmonary artery pressure (MPAP), CVP and, after balloon inflation, the PCWP were taken at end-expiration, with patients in the supine position. Arterial and pulmonary artery (n=49) or central venous blood samples (n=18) were obtained for determinations of Hb/Hct (Sysmex SE-9000, Sysmex Corporation, Kobe, Japan) and partial O_2 pressure/saturation (Rapidlab 865, Bayer Diagnostics, Tarrytown, NY, USA). The COP was measured by a membrane osmometer (Osmomat 050, Gonotex, Berlin, Germany, molecular cut-off at 20 kDa). Venous admixture was calculated from arterial, mixed (or central) venous and capillary O_2 contents, calculated from hemoglobin, O_2 pressures and saturations, according to standard formulae. The inspiratory O_2 fraction (F_iO_2), PEEP (cm H_2O), tidal volume and inspiratory plateau pressure were taken from the ventilator. The total respiratory compliance was calculated from tidal volume/(plateau pressure-PEEP), mL/cm H_2O. The chest X-ray was scored by a consultant radiologist, blinded to the study, who evaluated the number of quadrants with alveolar consolidations, ranging from 0 to 4. To further document the severity of the pulmonary abnormalities, a lung injury score (LIS) was calculated, taking into account the level of PEEP, the arterial PO_2/F_iO_2 ratio, to total respiratory compliance and the number of quadrants with alveolar

consolidations on the chest radiograph (34). The score ranges from 0 to 4, with values below 2.5 denoting ALI and above 2.5 ARDS.

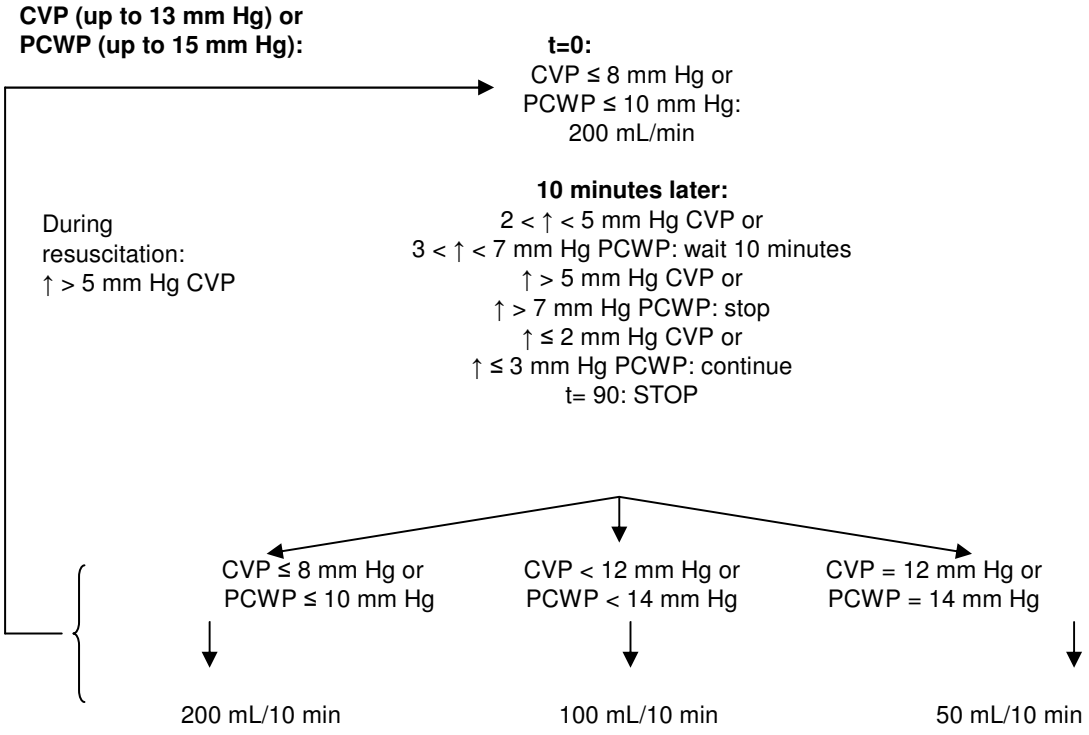

Figure 1. Fluid challenge protocol (modified from reference 30).

Patients had been randomly assigned to NaCl 0.9%, Gelofusine^{R} (gelatin 40g/L, B. Braun Melsungen AG, Germany, in 154/120 mmol/L NaCl), HES 6% (MW 200.000, substitution 0.45-0.55, Hemohes^{R}, B. Braun Melsungen AG, Germany, in saline) or albumin 5% (100 mL Cealb 20%, Sanquin, CLB, Amsterdam, The Netherlands, diluted in 300 mL of saline). After baseline measurements, fluids were given during 90 min on the basis of the response within predefined pressure limits, on the basis of the PCWP after appropriate wedging (n=36) or the central venous pressure (n=31), according to a fluid challenge protocol described in the literature (ref. 30, Figure 1) and targeting to a maximum PCWP of 15 mm Hg and a CVP of 13 mm Hg. Boluses of maximum 200 mL were given per 10 min, so that the maximum fluid challenge was 1800 mL in 90 min. Concomitant treatment, including ventilatory settings and administration of vasoactive and sedative drugs was unchanged. The measurements were repeated immediately after completing the fluid challenge (t=90 min). Diuresis

was recorded.

Statistical analysis. The CO and ITBV were indexed to body surface area, yielding cardiac index (CI) and intrathoracic blood volume index (ITBVI), respectively. EVLW was expressed as EVLW/kg body weight. Since we were primarily interested in the effect of colloid and the intrinsic effects of HES and albumin, we evaluated with help of the non-parametric Mann Whitney U test if there were statistically significant differences between saline and (pooled) colloid fluid loading, and between HES or albumin versus gelatin loading. Baseline and changes from baseline were evaluated, after studying changes in the whole group with help of the paired non-parametric Wilcoxon signed rank test. We have indicated four levels of significance, $P<0.05$, 0.01, 0.005 and 0.001 to account for multiple testing. Spearman rank correlation coefficients were used to express relations. Data are presented as median and range. The study was powered to detect a PLI and EVLW difference between saline (n=14) and colloid fluid resuscitation (n=40) of 22% (at a standard deviation of 25%), at two-sided $\alpha=0.05$ and $ß=0.80$.

RESULTS

Patient characteristics. Patient characteristics are listed in Table 1. Patients had an uneventful recovery except for one cardiac surgery patient in the gelatin group, who eventually died from postoperative complications (cerebral infarction), and one vascular surgery patient in the saline group, who died one day post-operatively from re-bleeding. Both events were judged not to relate to fluid loading. Groups were comparable, except for sex distribution. Except for one patient with ARDS (LIS >2.5, in the saline group) all patients had ALI. More saline than colloid fluid was administered.

Hemodynamic and biochemical variables. There were no baseline differences. Fluid loading increased CVP, MPAP (n=49) and PCWP (n=36) (P values in Table 2). CVP and PCWP changes interrelated ($r_s=0.61$, $P<0.001$). CI increased more in the colloid than in the saline groups. Saline loading decreased COP and colloid loading increased it. Hct decreased in the colloid groups and remained unchanged in the saline group, so that plasma volume rose more in the former.

Table 2. Hemodynamic and biochemical changes

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
CVP, mm Hg				
t=0	4 (1-12)	4 (0-8)	3 (0-7)	5 (1-9)
t=90[1]	5 (2-13)[c]	7 (3-11)	7 (4-12)	8 (4-12)
PCWP, mm Hg	n=9	n=6	n=9	n=12
t=0	6 (4-13)	7 (3-10)	7 (3-11)	7 (1-10)
t=90[1]	9 (5-15)[a]	11 (7-14)	12 (9-15)	11 (8-14)
MPAP, mm Hg	n=12	n=11	n=13	n=13
t=0	16 (11-23)/12	16 (9-19)/11	16 (12-28)/13	17 (8-22)
t=90[1]	17 (12-29)[c]	22 (14-26)	24 (17-35)	22 (15-26)
CI, L/min/m^2				
t=0	3.0 (2.1-4.5)	3.1 (2.2-4.8)	2.7 (1.6-4.4)	3.0 (2.4-4.7)
t=90[1]	3.1 (1.8-5.8)[b]	3.9 (3.5-4.8)	3.9 (2.8-6.2)	3.8 (2.6-5.9)
ITBVI, mL/min/m^2	n=14	n=10	n=14	n=16
t=0	1119 (689-1371)	1171 (938-1605)	1177 (716-1953)	1049 (641-1387)
t=90[1]	1150 (793-1513)	1277 (852-3315)	1181 (772-2164)	1189 (741-1530)
COP, mm Hg				
t=0	16.8 (10.5-20.6)	17.9 (13.3-21.1)	18.1 (13.5-24.9)	18.1 (13.0-23.8)
t=90[1]	15.4 (9.5-22.9)[c]	19.8 (18.3-24.7)	21.7 (17.5-25.5)	21.2 (15.0-25.8)
Hemoglobin, mmol/L				
t=0	6.0 (4.2-7.5)	5.8 (4.3-7.7)	6.0 (3.7-8.9)	5.5 (4.4-9.1)
t=90[1]	6.0 (4.7-7.2)[c]	5.1 (4.0-6.4)	5.0 (3.7-7.5)	4.9 (4.3-7.8)
Hematocrit				
t=0	0.28 (0.20-0.35)	0.28 (0.21-0.35)	0.28 (0.17-0.42)	0.26 (0.20-0.42)
t=90[1]	0.28 (0.22-0.34)[c]	0.24 (0.18-0.29)	0.24 (0.16-0.36)	0.23 (0.20-0.37)
Change in plasma volume, %				
t=0-90	3.0 (-17.5-24.5)[c]	19.6 (-7.7-49.4)	20.5 (-10.8-49.6)	14.9 (2.3-42.6)

Median (ranges) or number (N) where appropriate. Abbreviations: CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; MPAP = mean pulmonary artery pressure; CI = cardiac index; ITBVI = intrathoracic blood volume index; COP = colloid osmotic pressure; [1]P<0.001 for whole group at t=90 versus t=0 min; [a]P<0.05, [b]P<0.005, [c]P<0.001 for change in saline versus colloids.

Pulmonary leak index and extravascular lung water. Technical problems precluded PLI measurements in 3 patients. EVLW (and ITBV) measurements were available in 14 patients in the saline, 10 patients in the gelatin, 14 patients in the HES and 16 patients in the albumin group. Baseline PLI and EVLW were above normal in 9 (56%) and 5 (31%) of patients in the saline group, 7 (44%) and 2 (13%) of patients in the gelatin group, 13 (76%) and 5 (29%) of patients in the HES group and 11 (61%) and 8 (44%) of patients in the albumin group, and cardiac and major vascular surgery patient groups did not differ. The baseline PLI was thus above normal (> 14.7 x 10^{-3}/min) in 40 of 67 (60%) patients and the baseline EVLW in 20 of 67 (30%) patients, without significant group differences. The PLI decrease in HES was greater than in the gelatin group (Figure 2). Whereas EVLW declined for all

groups together (P<0.05), the change did not differ between saline and colloid fluid resuscitation, whether the PLI was elevated or not (Figure 3). The changes in EVLW directly correlated with changes in PCWP (r_s=0.43, P<0.05).

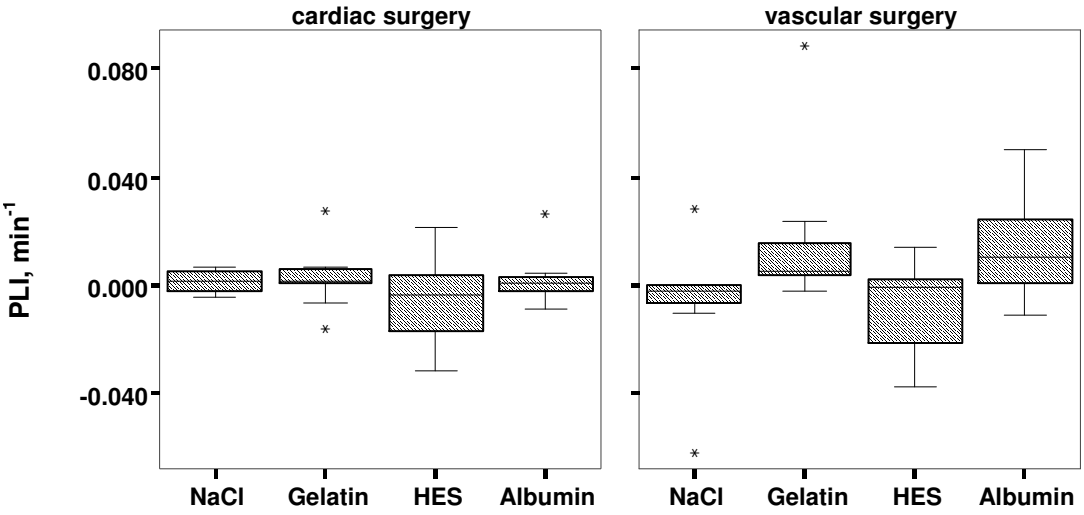

Figure 2. Box and whisker plots of changes in pulmonary leak index ($PLI_{t=90}$-$PLI_{t=0}$, x 10^{3}·min^{-1}) in the various resuscitation fluid groups within cardiac surgery patients and vascular surgery patients. There was no difference among groups, except for a greater decline in the HES than the gelatin group (P<0.05). Values in boxes are at 25th percentile, median and 75th percentile (= interquartile range, IQR); whiskers are values <1.5 IQR and extremes (*, at >3 IQR), where appropriate.

Respiratory variables (Table 3). At baseline, the F_iO_2 in the saline group was 50 (39-62), in the gelatin group 41 (37-61), in the HES group 41 (39-60) and in the albumin group 40 (38-60)% (NS). The PEEP at baseline was 6 (5-15), 7 (5-12), 5 (4-10) and 7 (5-16) cm H_2O and the tidal volumes were 600 (500-730), 580 (450-740), 571 (400-730) and 566 (395-1110) mL, in the saline, gelatin, HES and albumin groups, respectively (NS). During fluid loading, the P_vO_2, P_aO_2 and oxygenation ratio increased in all groups, while the P_aCO_2 (not shown) did not change. In the patients receiving colloids, a small elevation in LIS was associated with a decrease in total respiratory compliance. The fall in compliance correlated with the rise in ITBVI (r_s=0.28, P<0.05).

Table 3. Respiratory variables

	NaCl 0.9% n=16	Gelatin 4% n=16	HES 6% n=17	Albumin 5% n=18
Temperature, °C				
t=0	36.3 (34.9-37.1)	35.9 (34.9-36.6)	35.6 (34.5-37.2)	35.6 (35.0-37.1)
t=90[4]	36.4 (34.8-37.3)	36.2 (35.3-37.2)	35.9 (35.1-38.4)	36.0 (35.1-37.9)
P_aO_2, mm Hg				
t=0	127 (87-172)	116 (70-185)	130 (66-220)	113 (76-189)
t=90[2]	142 (82-195)	131 (78-190)	143 (82-217)	134 (74-179)
P_vO_2, mm Hg				
t=0	41 (30-75)	40 (31-54)	36 (24-50)	38 (28-50)
t=90[2]	40 (36-51)	38 (33-88)	41 (27-46)	40 (30-64)
P_aO_2/F_iO_2, mm Hg				
t=0	279 (140-430)	281 (121-463)	289 (110-537)	263 (127-485)
t=90[4]	337 (164-488)	324 (134-475)	308 (161-529)	333 (123-459)
Venous admixture				
t=0	0.21 (0.10-0.62)	0.19 (0.09-0.40)	0.17 (0.04-0.34)	0.16 (0.05-0.40)
t=90	0.16 (0.09-0.32)	0.16 (0.06-0.38)	0.19 (0.06-0.36)	0.16 (0.07-0.36)
Plateau pressure, cm H_2O				
t=0	18 (13-28)	18 (12-26)	18 (14-22)	18 (14-33)
t=90[3]	18 (14-28)	20 (12-27)[c]	19 (15-28)[c]	18 (14-26)[c]
Total respiratory compliance, mL/cm H_2O				
t=0	63 (28-91)	49 (35-94)	50 (38-71)	53 (31-91)
t=90[4]	64 (26-91)[a]	48 (32-91)	46 (25-64)	53 (27-79)
Radiology number, quadrants				
t=0	0 (0-3)	1 (0-3)	0 (0-3)	0 (0-1)
t=90[1]	0 (0-4)	0.5 (0-4)	1 (0-3)	1 (0-3)
Lung injury score				
t=0	1.00 (0.25-2.75)	1.12 (0.25-2.00)	1.00 (0.25-2.00)	0.75 (0.25-2.00)
t=90[1]	1.00 (0.25-2.75)[b]	1.25 (0.50-2.75)	1.00 (0.50-2.25)	1.00 (0.25-2.50)
EVLW, mL/kg				
t=0	6.1 (4.8-13.2)	5.9 (3.7-20.0)	6.7 (2.5-13.8)	6.8 (2.1-10.3)
t=90[1]	6.1 (3.9-13.3)	5.2 (4.0-21.5)	6.2 (3.2-12.1)	6.2 (1.5-13.0)
PLI, x 10^{-3}/ min				
t=0	15 (6-101)	14 (6-73)	24 (11-81)	20 (7-60)
t=90	15 (10-50)	15 (10-98)	20 (9-48)[d]	21 (7-103)

Median (ranges) or number (N) where appropriate. Abbreviations: PO_2 = partial pressure of O_2 in arterial (a) or venous (v) blood; F_iO_2 = inspiratory O_2 fraction; EVLWI = extravascular lung water index; PLI = pulmonary leak index; [1]P<0.05, [2]P<0.01, [3]P<0.005, [4]P<0.001 for whole group at t=90 versus t=0 min; [a]P<0.05, [b]P<0.001 for change in saline versus colloids; [c]P<0.01 for change between colloid groups; [d]P<0.05 for change between gelatin and HES.

DISCUSSION

Many patients after cardiac or major vascular surgery had some degree of ALI, associated with increased permeability, edema, and ventilatory and radiographic abnormalities in the lungs. While fluid overloading was prevented, the changes were not affected by loading with saline, gelatin, HES or albumin. However, HES

attenuated increased permeability. Nevertheless, the LIS slightly increased in the colloid groups, associated with a fall in total respiratory compliance.

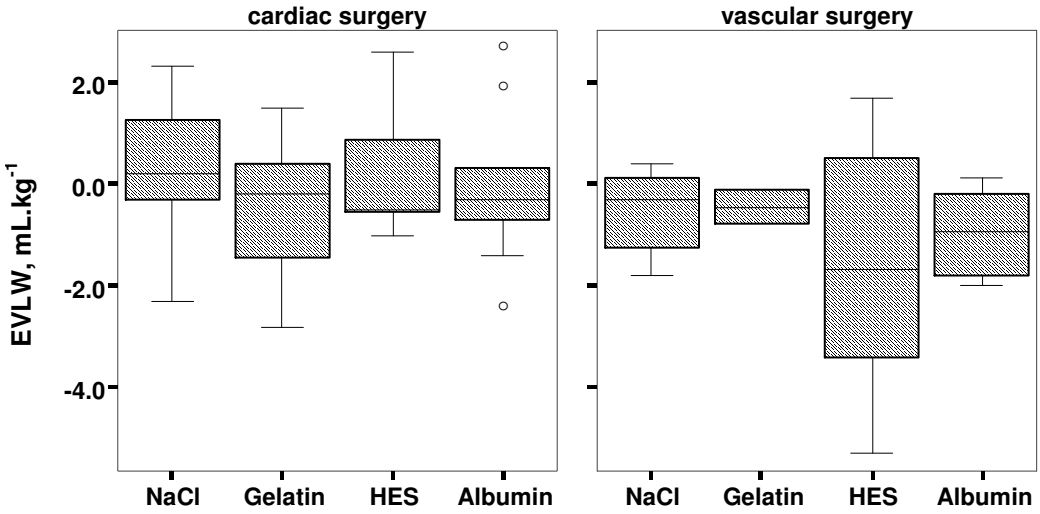

Figure 3. Box and whisker plots of changes in extravascular lung water ($EVLW_{t=90}$-$EVLW_{t=0}$) in the various resuscitation fluid groups within cardiac and vascular surgery patients. There was no difference between groups, while for all patients together EVLW decreased ($P<0.05$). Values are at 25th percentile, median and 75th percentile (IQR); whiskers are values <1.5 IQR and outliers (1.5 <outlier (○) <3 IQR), where appropriate.

In our study, 60% of the patients had an increase in the PLI directly after surgery, confirming that cardiac and major vascular surgery are risk factors for capillary injury and ALI (14-18). Indeed, 30% of the patients had an EVLW of more than 7 mL/kg directly after surgery, agreeing with the literature, showing a moderate and transient increase in EVLW in some patients after cardiac or major vascular surgery (9,10,19-22,31).

Since diuresis was similar, the EVLW did not change in either group and plasma volume increased less in the saline group than in the colloid groups, the extrapulmonary extravascular fluid volume must have been higher in the saline group than in the colloid groups. Hence, the plasma COP increase in colloid-treated patients was effective in keeping colloid fluids, at least temporarily within the plasma volume compartment with less extravasation into the extrapulmonary extravascular

space, as compared to saline loading. The rise in systemic venous pressure was apparently able to increase fluid extravasation in the systemic circulation during fluid loading, which was limited by a concomitant increase in COP in the patients receiving colloids. Apparently, COP remained operative, even though it is widely accepted that cardiac surgery evokes a systemic inflammatory response and cardiac and vascular surgery are accompanied by ischemia/reperfusion, contributing to an increase in capillary permeability (14,15,18). Increased extravascular accumulation of saline as compared to colloid fluids apparently did not include the lungs.

The lack of effect of COP on PLI and EVLW in our study agrees with the findings by Sibbald and co-workers (2), describing transvascular small and large molecular tracer flux in ALI/ARDS patients, loaded with albumin, and the predominant effect of hydrostatic pressure rather than of COP on these fluxes, at least when permeability was severely increased, as in the experimental oleic acid model (4). That transvascular albumin transport increased with albumin loading in their study but not in ours, can be explained, since the PLI method in our study takes intravascular albumin mass and surface area into account and is a specific measure of permeability independent of bulk flow (14). Our results do not agree with experimental studies showing a benefit of colloid versus saline fluid loading regarding edema formation in injured lungs (3). In contrast to those studies, the increase in permeability may have been more severe in our patients, or hydrostatic pressures promoting edema formation may have been lower than in the experiments, or both. Otherwise, the unchanged PLI during a rise in CI may agree with the literature showing that an increase in CI does not increase protein permeability in the isolated dog lung (35). Although lung water may increase with increased CI and surface area available for exchange in the isolated dog lung (35), lung edema is CI-independent when evaluated in the in vivo lung injured by oleic acid or in humans after cardiac surgery (32,36). In our study, a maximum PCWP of 10-15 mm Hg, at a PEEP of 4-16 cm H_2O, was well tolerated, even though the changes in EVLW between t=0 and 90 min directly correlated with changes in PCWP rather than with changes in PLI or COP. The latter indeed suggests an important role of hydrostatic pressure in the formation of pulmonary edema in ALI after major surgery and the

protective role of avoiding high filling pressures on the formation of edema, even when permeability is increased and COP is lowered. Conversely, our results show the safety of the fluid challenge protocol (30), whether CVP or PCWP are used. Indeed, the fair interrelation between CVP and PCWP changes in our patients agrees with the literature (37).

In spite of an increased oxygenation ratio, the LIS slightly but significantly increased, but more in colloid groups than in the saline group, because of a greater decline in total respiratory compliance in the colloid groups. Since changes in compliance were associated with changes in ITBVI that includes pulmonary blood volume, a fall in compliance may relate to greater pulmonary intravascular filling with colloids. Indeed, volume loading in pigs decreased total respiratory compliance, and exsanguination of dogs/pigs increased pulmonary compliance due to a loss of pulmonary blood volume (38,39). Finally, the greater rise in CI in the colloid groups versus the saline group can be explained by greater expansion of the plasma volume tending to elevate the ITBVI, determining the preload of the heart (22,31), with colloids than with crystalloids. These disparate hemodynamic effects agree with the literature, showing that crystalloids were less effective expanders of plasma volume and in boosting cardiac output after cardiac or major vascular surgery, than colloids (6,8,9,11,13,22,40). The increase in arterial PO_2 can be explained by a rise in venous PO_2, concomitantly with a rise in CI and tissue oxygenation, at constant venous admixture, and to the concomitant slight fall in EVLW with time (41). Alternatively, the increase in PO_2 may be associated with opening up of postoperatively increased atelectatic areas, with increasing airway pressures.

Finally, there is evidence in our study that HES favourably affects pulmonary permeability, independent of COP, in ALI after cardiac surgery or major vascular surgery. This agrees with experimental studies, suggesting that middle and high molecular weight starch molecules may ameliorate lung injury and permeability-edema under a variety of circumstances, including ischemia/reperfusion, endotoxemia, toxic injury and extracorporeal bypass (23-27). Rittoo and co-workers described better pulmonary function after aortic surgery in patients treated with HES

than with gelatins, but did not study permeability or edema directly (28). Some caution is warranted, however, as some patients underwent thoracic procedures in the HES group and baseline PLI tended to be somewhat higher than in the gelatin group. We could not confirm the experimental observations that albumin solutions have antioxidant properties and may ameliorate endothelial-neutrophil interactions in the lungs and permeability edema (29). Since our study was primarily powered to detect a difference between saline and colloid fluid loading, the number of patients studied may have been too small to demonstrate a small specific effect of albumin.

Although having the advantage of a multiple comparison among fluids in a relatively large patient group and independent measurements of permeability and edema, our study carries some limitations. The study was not investigator-blinded. Fluid resuscitation was guided by filling pressures, which is common practice since hydrostatic pressures are important determinants of EVLW. However, we believe that the conclusion that EVLW does not depend on the type of fluid given within this range of hydrostatic pressures is clinically relevant. We cannot exclude however, that more saline would have been needed and more EVLW had developed, as compared to colloid fluid, if fluid loading had been guided by filling volumes (ITBV) rather than pressures. Thermal-dye EVLW may be underestimated when focal lung injury is accompanied by regional hypoperfusion (42). However, the underestimation and CI-dependency of EVLW in hypoperfused areas may be minimal in less severe, indirect, lung injury in humans as opposed to animal models of ARDS (32,42). There are only few studies utilizing direct measurements of EVLW, often with help of old techniques and ex vivo dye concentration measurements, and their response to multiple fluids after cardiac or major vascular surgery (9-11,19,20,22,31). In other studies, only surrogate indicators of pulmonary edema have been used (6-8,12,13,28,40). The number of fluids evaluated in the studies has often been limited to two or three, so that the potential intrinsic properties of fluids could not be easily separated from effects caused by COP changes. Gallagher and co-workers compared saline, HES and albumin (n=5 in each group) postoperatively and did not find differences in EVLW (elevations) (10). Karanko and co-workers compared dextran (n=14) with Ringer's acetate (n=18) for fluid loading after cardiac surgery and found that EVLW

did not increase in both groups, while gas exchange transiently deteriorated in the dextran group (11). Wahba and co-workers found that gelatin loading (n=11) increased ITBVI and thus CI more than Ringer's solution (n=11) after cardiac surgery, without affecting EVLW, as in our study (22). Studying aortic surgery patients, Shires and co-workers compared Ringer's lactate with a colloid (plasmanate) in 18 patients during surgery, and despite differences in COP, EVLW after surgery did not differ (9). As in our study, this can be explained by the relatively low filling pressure attained (9). Our study thus extends some of these previous studies and may conform the conclusion from meta-analyses that the type of fluid used for treating hypovolemia does not effect pulmonary edema formation, provided that fluid overloading is avoided.

In conclusion, saline or colloids do not affect permeability-edema in ALI after cardiac or major vascular surgery, provided that fluid overloading is avoided, except for HES that may ameliorate increased permeability. The LIS, however, may slightly increase after colloid versus saline loading, because of greater intrathoracic plasma volume expansion decreasing total respiratory compliance, thus indicating that changes in LIS (and respiratory compliance) during fluid loading do not represent changes in permeability-edema.

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REFERENCES

1. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloid versus crystalloids for fluid resuscitation in critically ill patients. The Cochrane Database of Systematic Reviews 2004, issue 4, art no CD000567
2. Sibbald WJ, Driedger AA, Wells GA, Myers Lefcoe M. The short-term effects of increasing plasma colloid osmotic pressure in patients with non-cardiac pulmonary edema. Surgery 1983; 93: 620-636
3. Finch JS, Reid C, Bandy K, Fickle D. Compared effects of selected colloids on extravascular lung water in dogs after oleic acid-induced lung injury and severe hemorrhage. Crit Care Med 1983; 11: 267-270

4. Pearl RG, Halperin BD, Mihm FG, Rosenthal MH. Pulmonary effects of crystalloid and colloid resuscitation from hemorrhagic shock in the presence of oleic-induced pulmonary capillary injury in the dog. Anesthesiology 1988; 68: 12-20
5. The SAFE study investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350: 2247-2256
6. Skillman JJ, Restall S, Salzman EW. Randomized trial of albumin vs electrolyte solutions during abdominal aortic operations. Surgery 1975; 78: 291-303
7. Boutros AR, Ruess R, Olson L, Hoyt JL, Baker WH. Comparison of hemodynamic, pulmonary, and renal effects of use of three types of fluid after major surgical procedures on the abdominal aorta. Crit Care Med 1979; 7: 9-13
8. Virgilio RW, Rice CL, Smith DE, et al. Crystalloid vs. colloid resuscitation: Is one better? Surgery 1979; 85: 129-139
9. Shires GT, Peitzman AB, Albert SA, et al. Response of extravascular lung water to intraoperative fluids. Ann Surg 1983; 197: 515-519
10. Gallagher JD, Moore RA, Kerns D, et al. Effects of colloid or crystalloid administration on pulmonary extravascular lung water in the postoperative period after coronary bypass grafting. Anesth Analg 1985; 64: 753-758
11. Karanko MS, Klossner JA, Laaksonen VO. Restoration of volume by crystalloid versus colloid after coronary bypass: hemodynamics, lung water, oxygenation, and outcome. Crit Care Med 1987; 15: 559-566
12. London MJ, Ho JS, Triedman JK, et al. A randomized clinical trial of 10% pentastarch (low molecular weight hydroxyethyl starch) versus 5% albumin for plasma volume expansion after cardiac operations. J Thorac Cardiovasc Surg 1989; 97: 785-797
13. Tølløfsrud S, Svennevig JL, Breivik H, et al. Fluid balance and pulmonary functions during and after coronary artery bypass surgery: Ringer's acetate compared with dextran, polygeline, or albumin. Acta Anaesthesiol Scand 1995; 39: 671-677
14. Raijmakers PGHM, Groeneveld ABJ, Schneider AJ, et al. Transvascular transport of ^{67}Ga in the lungs after cardiopulmonary bypass surgery. Chest 1993; 104: 1825-1832
15. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, et al. Transient increase in interleukin-8 and pulmonary microvascular permeability following aortic surgery. Am J Respir Crit Care Med 1995; 151: 698-705
16. Groeneveld ABJ, Raijmakers PGHM. The ^{67}Gallium-transferrin pulmonary leak index in patients at risk for the acute respiratory distress syndrome. Crit Care Med 1998: 26: 685-691
17. Pararajasingam R, Nicholson ML, Bell PRF, Sayers RD. Non-cardiogenic pulmonary oedema in vascular surgery. Eur J Vasc Endovasc Surg 1999; 17: 93-105
18. Ng CSH, Wan S, Yim APC, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest 2002; 121: 1269-1277

19. Byrick RJ, Kay JC, Noble WH. Extravascular lung water accumulation in patients following coronary artery surgery. Canad Anaesth Soc J 1977; 24: 332-345
20. Sivak ED, Starr NJ, Graves JW, Cosgrove DM, Borsh J, Estafanous GE. Extravascular lung water values in patients undergoing coronary artery bypass surgery. Crit Care Med 1982; 10: 593-596
21. Lumb PD. A comparison between 25% albumin and 6% hydroxyethyl starch solutions on lung water accumulation during and immediately after cardiopulmonary bypass. Ann Surg 1987; 26: 210-213
22. Wahba A, Sendtner E, Strotzer M, Wild K, Birnbaum DE. Fluid therapy with Ringer's solution versus Haemacel following coronary artery bypass surgery. Acta Anaesthesiol Scand 1996; 40: 1227-1233
23. Tanaka H, Dahms TE, Bell E, Naunheim KS, Baudendistel LJ. Effect of hydroxyethyl starch on alveolar flooding in acute lung injury in dogs. Am Rev Respir Dis 1993; 148: 852-859
24. Nielsen VG, Tan S, Brix AE, Baird MS, Parks DA. Hextend (hetastarch solution) decreases multiple organ injury and xanthine oxidase release after hepatoenteric ischemia-reperfusion in rabbits. Crit Care Med 1997; 25: 1565-1574
25. Axon RN, Baird MS, Lang JD, Brix AE, Nielsen VG. Pentalyte decreases lung injury after aortic occlusion-reperfusion. Am J Respir Crit Care Med 1998; 157: 1982-1990
26. Chiang C-H, Wu C-P, Perng W-C, Yan H-C, Yu C-P. Dexamethasone and pentastarch produce additive attenuation of ischemia/reperfusion lung injury. Clin Sci 2000; 99: 413-419
27. Tian J, Lin X, Guan R, Xu J-G. The effects of hydroxyethyl starch on lung capillary permeability in endotoxic rats and possible mechanisms. Anesth Analg 2004; 98: 768-774
28. Rittoo D, Gosling P, Burnley S, et al. Randomized study comparing the effects of hydroxyethyl starch solution with Gelofusine on pulmonary function in patients undergoing aortic aneurysm surgery. Br J Anaesth 2004; 92: 61-66
29. Powers KA, Kapus A, Khadaroo RG, Papia G, Rotstein OD. 25% albumin modulates adhesive interactions between neutrophils and the endothelium following shock/resuscitation. Surgery 2002; 132: 391-398
30. Weil MH, Henning RJ. New concepts in the diagnosis and fluid treatment of circulatory shock. Thirteenth Annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture. Anesth Analg 1979; 58: 124-132
31. Gödje O, Peyerl M, Seebauer T, Dewald O, Reichart B. Reproducibility of double indicator dilution measurements of intrathoracic blood volume compartments, extravascular lung water, and liver function. Chest 1998; 113: 1070-1077
32. Boldt J, Kling D, von Bormann B, Scheld HH, Hempelmann G. Influence of cardiac output on thermal-dye extravascular lung water (EVLW) in cardiac patients. Intensive Care Med 1987; 13: 310-314

33. Johansen LB, Bie P, Warberg J, et al. Hemodilution, central blood volume, and renal responses after an isotonic saline infusion in humans. Am J Physiol 1997; 272: R549-R556
34. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138: 720-723
35. Ehrhart IC, McCloud LL, Orfanos SE, Catravas JD, Hofman WF. Effect of high blood flow on pulmonary vascular permeability to protein. J Appl Physiol 1994; 76: 2342-2347
36. García-Delgado M, Colmenero-Ruiz M, Fernández-Sacristán MA, Rus-Mansilla C, Fernández-Mondéjar E. Effect of catecholamine-induced increase in cardiac output on extravascular lung water. Crit Care Med 2001; 29: 931-935
37. Rice CL, Hobelman CF, John DA, et al. Central venous pressure or pulmonary capillary wedge pressure as the determinant of fluid replacement in aortic surgery. Surgery 1978; 84: 437-440
38. Mutoh T, Lamm WJE, Embree LJ, Hildebrandt J, Albert RK. Volume infusion produces abdominal distension, lung compression, and chest wall stiffening in pigs. J Appl Physiol 1992; 72: 575-582
39. Colebatch HJH, Ng CKY, Berend N, Maccioni FJ. Effect of the chest wall and blood volume on pulmonary distensibility. J Appl Physiol 1992; 72: 186-193
40. Zetterström H. Albumin treatment following major surgery. II. Effects on postoperative lung function and circulatory adaptation. Acta Anaesth Scand 1981; 25: 133-141
41. Nirmalan M, Willard T, Columb MO, Nightingale P. Effect of changes in arterial-mixed venous oxygen content difference ($C(a\text{-}v)O_2$) on indices of pulmonary oxygen transfer in a model ARDS lung. Br J Anaesth 2001; 86: 477-485
42. Groeneveld ABJ, Verheij J. Is pulmonary edema associated with a high extravascular thermal volume? Crit Care Med 2004; 32: 899-901

CHAPTER 7

DISCUSSION

FIRST PART: Pulmonary dysfunction in the critically ill

In the first part of this thesis, we studied the incidence and pathogenesis of pulmonary dysfunction in three subsets of patients at risk for developing acute lung injury (ALI) and adult respiratory distress syndrome (ARDS), i.e. post-operative cardiac surgery patients (**chapter 2**), major vascular surgery patients (**chapter 3**) and septic patients (**chapter 4**). We focused on the relative contribution to acute lung injury of pulmonary edema and increases in endothelial permeability, measured as the efflux of radiolabelled transferrin by the pulmonary leak index (PLI), in relation to oxygenation and radiological abnormalities.

In patients after cardiac surgery and major vascular surgery and in septic patients, gas exchange, lung mechanical abnormalities and a fall in oxygenation were not directly related to the presence of extravascular lung water (EVLW). Moreover, supranormal values of the pulmonary leak index (PLI) were not associated with more radiographic densities, mechanical abnormalities or lower oxygenation levels after cardiac or major vascular surgery. However, in septic patients, particularly if associated with pneumonia, increases in pulmonary microvascular permeability were present together with more radiographic pulmonary densities, higher values of shunting and cardiac index and lower oxygenation ratios, independently of EVLW or the presence of atelectasis.

An increase in pulmonary microvascular permeability, as measured by the PLI, might be transient, particularly after uncomplicated surgery (1). Indeed, 44% of the patients after cardiac and 69% of the patients after major vascular surgery had an increase in PLI. However, no sustained pulmonary complications occurred and all but two patients were discharged from the ICU the next morning, suggesting that increased permeability was transient in these patients. In contrast, all septic patients had a supranormal PLI, as well as higher values of PLI and more sustained ventilatory problems, related to more severe microvascular injury. Moreover, high levels of PLI were associated with a higher mortality rate in septic patients.

Increases in EVLW were found in approximately 30% of the post-operative cardiac and aortic surgery patients, and in 68% of the septic patients, but EVLW was not associated with outcome. Moderate increases in extravascular lung water however, may be located in interstitial areas not important for gas exchange, thereby explaining the absence of a direct relationship between the moderate increases in EVLW and gas exchange, as seen in our patients.

The importance of the colloid osmotic pressure in preventing the development of lung edema decreases in the presence of an increase in pulmonary microvascular permeability, as the colloid-osmotic gradient between the intravascular and interstitial compartments decreases. This explains our finding that the COP related to the amount of EVLW in postoperative cardiac surgery patients, but not in the vascular surgery and septic patients, the latter groups having a higher incidence and higher levels of PLI. In the vascular surgery patients a direct relationship was found between increases in microvascular permeability (PLI) and the development of EVLW, but this remained without direct consequences on gas exchange. The absence of a relationship between the PLI and EVLW in the other groups may be due to pulmonary protection mechanisms to prevent the development of lung edema, including an increase in lymph flow for instance, together with changes in interstitial hydrostatic and colloid osmotic pressures.

Absent relationships between the EVLW and PLI on the one hand and gas exchange and radiological abnormalities on the other hand point towards a role of atelectasis and/or consolidations in disturbing gas exchange. Indeed, atelectasis found after cardiac surgery was associated to higher levels of venous admixture, higher levels of positive end-expiratory pressure (PEEP) and oxygen inspiratory fraction (F_iO_2). Atelectasis was described to occur in almost all patients undergoing general anesthesia and intraoperative or perioperative lung recruitment may improve outcome (2). In the septic group of patients however, patients with and without atelectasis did not differ in gas exchange variables or number of quadrants with alveolar densities. In these patients, venous admixture related to the degree of microvascular injury (PLI), and in patients with pneumonia higher values of PLI were

found as compared to extrapulmonary sepsis, together with more extensive radiographic densities, higher venous admixture and cardiac index and lower oxygenation ratios.

Conclusion

Acute lung injury and the adult respiratory distress syndrome are conditions with a multi-factorial pathogenesis (Fig. 1). Measurement of interstitial edema (EVLW) and pulmonary microvascular permeability in the critically ill are valuable tools in evaluating the severity of the disease and their relative contribution to pulmonary dysfunction. Although pulmonary edema and microvascular injury are common after cardiac and major vascular surgery, atelectasis is, at least in part, determining radiological and ventilatory abnormalities and may be treated with lung recruitment maneuvers. However, in patients with sepsis, particularly if associated with pneumonia, increased venous admixture and impaired oxygenation are better explained by a lung vascular injury, associated with alveolar consolidations bearing no relationship to the presence of edema or atelectasis. This may hamper alveolar recruitment and limit the effect of diuretics and may imply the need for anti-inflammatory strategies.

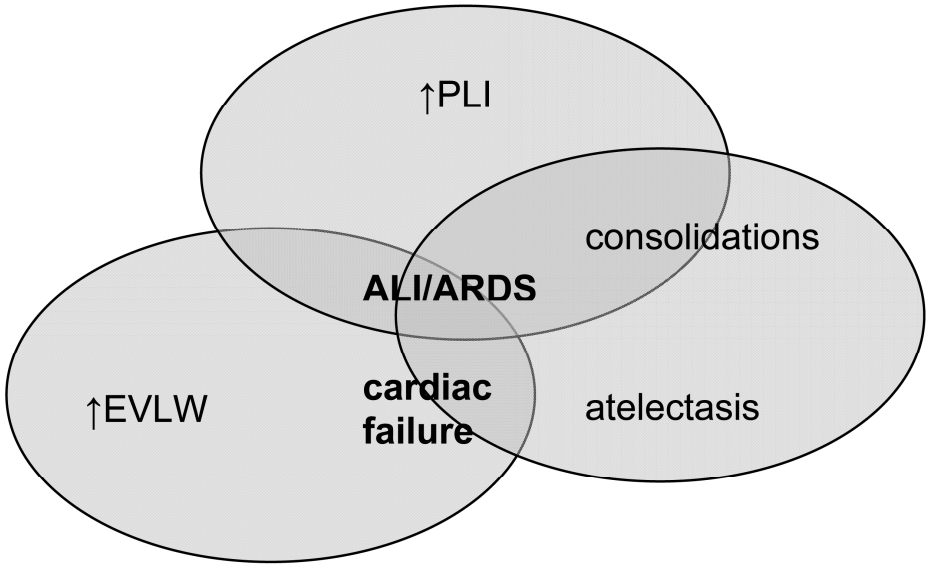

Figure 1. In the critically ill, acute lung injury and adult respiratory distress syndrome are conditions with a multi-factorial pathogenesis and characterized by radiological and gas exchange abnormalities, together with an increase in endothelial permeability. Patients with cardiac failure also may exhibit lung edema, radiological abnormalities and impaired oxygenation in the presence of an unchanged pulmonary leak index. Atelectasis and consolidations are not accompanied by increased PLI/EVLW or EVLW only, respectively.

SECOND PART: Fluid loading in the critically ill

In patients with ALI, treatment consists of supportive strategies, including mechanical ventilation to improve gas exchange. Furthermore, hypovolemia is relatively common in these patients, resulting in a reduction in oxygen delivery, the latter depending on both cardiac output and arterial oxygen content. Resuscitation fluids are needed to increase cardiac output and consequently oxygen delivery.

In the second part of the study, we evaluated the hemodynamic efficacy (**chapter 5**) of different resuscitation fluids relative to the pulmonary side effects (**chapter 6**). We studied the importance of the COP in plasma volume expansion and preventing pulmonary edema, together with possible intrinsic effects of fluids to influence myocardial contractility and microvascular permeability.

Our findings in the second part of this thesis show that colloids by their effect on the plasma COP are more effective in expanding plasma volume than saline, resulting in a greater increase in preload-recruitable cardiac and left ventricular stroke work indices. This may be of importance since recent studies show that fluid therapy guided by left ventricular stroke work volume may improve outcome (3,4). Second, changes in plasma COP associated with fluid resuscitation of either colloids or crystalloids do not affect extravascular lung water differently.

The major determinant of changes in EVLW appears to be a change in filling pressures, but at low levels of filling pressures no differences between the different fluid regimens were found. Since diuresis and the changes in EVLW were similar among groups and plasma volume increased less in the saline group than in the groups receiving colloids, the extrapulmonary extravascular fluid volume must have been higher in the patients receiving saline. This implies that the COP remains operative in the systemic circulation with less extravasation of colloids into the extrapulmonary extravascular space even in the presence of an increase in microvascular permeability. Moreover, this extravasation of saline explains why infusion of saline was less effective in increasing CI, LVSWI or filling pressures and

volumes as compared to infusion of colloids. The extravascular fluid accumulation of saline in the systemic circulation, but not in the pulmonary circulation may be explained by better protection mechanisms in the lungs, including an increase in lymph flow for instance. There was no change in the slope of the filling pressure to GEDVI relation, suggesting no differences in myocardial compliance and therefore in myocardial edema among the groups, even though COP was higher in colloid-loaded patients. These findings may imply that extravasation of saline occurs not in the myocardium or in the pulmonary interstitium, but in other organs and for example may cause intestinal edema (5). This is in line with the literature, in which organs were described to demonstrate large differences in capillary permeability, related to organ specific characteristics such as vascular reactivity, the degree of endothelial contraction and the composition of the capillary basement membrane (6).

Our study also suggests that HES may favourably affect pulmonary permeability, independent of the COP in ALI after cardiac or major vascular surgery, although the levels of PLI were higher at baseline in the HES patients with three patients in the HES group undergoing thoracic-abdominal surgery versus none in the gelatin group. The protective effect of HES agrees with experimental data demonstrating that starch molecules ameliorate microvascular permeability (7-9). We did not find an effect of albumin on endothelial permeability, in contrast to others (8), but the number of patients studied may have been too small.

Conclusions

In the treatment of hypovolemia, colloid fluid loading leads to a greater increase in preload-recruitable cardiac and left ventricular stroke work indices than saline, because of greater volume expansion following an increase in plasma colloid osmotic pressure. Provided that fluid overloading is prevented, the type of fluid does not affect pulmonary permeability and edema in patients with acute lung injury after cardiac or major vascular surgery, except for HES that may ameliorate increased permeability. Fluid loading based on filling pressures is safe, as long as the filling pressures targeted are lower than the threshold pressure for edema formation.

Future perspectives

Recent studies provide some evidence for the effectiveness of alternative approaches in the treatment of ALI/ARDS and measurement of EVLW and endothelial permeability may be valuable tools in the evaluation of new treatment strategies. In rats for instance, propofol was described to attenuate acute lung injury in an isolated rabbit-lung model (10) and anti-coagulant therapy was shown to attenuate the inflammatory response associated with I-R injury, thereby preventing organ dysfunction (11). Besides anti-inflammatory and anti-coagulant therapy, other treatment strategies include the administration of vasoactive drugs and promotion of alveolar fluid resorption (12). Perkins and coworkers demonstrated in a randomized trial that the use β-agonists in patients with ALI/ARDS, reduced lung water by increasing alveolar fluid resorption (13). Further research is needed to evaluate the short-term efficacy, together with the effects on outcome of these new treatment strategies in patients with acute lung injury, especially since ALI is associated with mortality in almost half of the patients (14). The precise contribution of atelectasis in different groups of critically ill also requires further study together with the evaluation of possible treatment strategies, including lung protective mechanical ventilation and lung recruitment.

With respect to fluid loading, new challenges include the study of the intrinsic properties of fluids in the ICU setting with the available techniques, as our study in vivo and others in vitro (7-9) point towards a possible favorable effect of starches in preventing increases in microvascular permeability.

REFERENCES

1. Raijmakers PGHM, Groeneveld ABJ, Rauwerda JA, Schneider AJ, Teule GJJ, Hack CE, Thijs LG. Transient increase in interleukin-8 and pulmonary microvascular permeability following aortic surgery. Am J Respir Crit Care Med 1995; 151: 698-705
2. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005; 102: 838-54
3. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995; 130: 423-429

4. Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. Anesth Analg 2005; 100: 1093-1106
5. Prien T, Backhaus N, Pelster F, Pircher W, Bünte H, Lawin P. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. J. Clin. Anesth. 1990; 2: 317-323
6. Plante GE, Chakir M, Ettaouil K, Lehoux S, Sirois P. Consequences of alteration in capillary permeability. Can J Physiol Pharmacol. 1996; 74: 824-33
7. Zikria BA, King TC, Stanford J, Freeman HP. A biophysiological approach to capillary permeability. Surg 1989; 105: 625-631
8. Nielsen VG, Tan S, Brix AE, Baird MS, Parks DA (1997) Hextend (hetastarch solution) decreases multiple organ injury and xanthine oxidase release after hepatoenteric ischemia-reperfusion in rabbits. Crit Care Med 25: 1565-1574
9. Chiang C-H, Wu C-P, Perng W-C, Yan H-C, Yu C-P. Dexamethasone and pentastarch produce additive attenuation of ischemia/reperfusion lung injury. Clin Science 2000; 99: 413-419
10. Yumoto M, Nishida F, Katsuya H. Propofol attenuates oxidant-induced acute lung injury in an isolated perfused rabbit-lung model. J Anesth 2005; 19: 287-294
11. Olanders K, Borjesson A, Zhao X, Andersson R. Effects of anticoagulant treatment on intestinal ischaemia and reperfusion injury in rats. Acta Anaesthesiol Scand 2005; 49: 517-24
12. Groeneveld AB. Vascular pharmacology of acute lung injury and acute respiratory distress syndrome. Vascul Pharmacol 2002; 39: 247-56
13. Perkins GD, McAuley DF, Thickett DR. The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 2006; 173: 281-287
14. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcome of acute lung injury. N Eng J Med 2005; 353: 1685-1693

SAMENVATTING

HART- EN LONGFUNCTIE VAN DE INTENSIVECAREPATIËNT EN HET EFFECT VAN VLOEISTOFBELASTING

Eerste deel: Longfalen op de intensive care

Longfalen is een veelvoorkomend probleem bij patiënten op de intensive care en wordt onder andere gekenmerkt door een verslechterde gasuitwisseling, afwijkingen op de röntgenfoto en longoedeem. Als longfalen plaatsvindt in de context van zogenaamde 'acute lung injury' (ALI), acute longschade, dan is een bijkomend kenmerk een verhoogde doorlaatbaarheid van de vaten ten gevolge van endotheelschade en kan de situatie uiteindelijk leiden tot het zogenaamde 'adult respiratory distress syndrome' (ARDS). Risicofactoren op het ontstaan hiervan zijn sepsis, trauma, hart- en centrale vaatchirurgie. Algemeen wordt aangenomen dat het teveel aan longwater (longoedeem) de gasuitwisseling in de long duidelijk kan verstoren. Longoedeem in geval van ALI en ARDS wordt permeabiliteitsoedeem genoemd en moet worden onderscheiden van longoedeem ten gevolge van hartfalen, een situatie waarbij longoedeem ontstaat door een verhoogde hydrostatische druk, maar waarbij de doorlaatbaarheid van de vaten intact is. Dit onderscheid is belangrijk voor de therapie van de patiënt. Zo zal bij longoedeem door hartfalen de therapie gericht worden op verbetering van de hartfunctie. De verhoogde doorlaatbaarheid van het endotheel leidt tot een verhoogde flux van vloeistof en eiwitten van het vaatbed naar het interstitium, hetgeen kan leiden tot interstitieel oedeem. De doorlaatbaarheid van de vaten kan worden gemeten door middel van permeabiliteitsmetingen met gelabeld ^{67}Gallium (Ga)-transferrine en ^{99m}Technetium, hetgeen resulteert in een zogenaamde 'pulmonary leak index' (PLI). De snelheid waarmee ^{67}Ga-transferrine lekt van het vaatbed naar het interstitium van de longen is dan een maat voor de doorlaatbaarheid van het vaatbed. In eerdere studies is reeds aangetoond dat met de PLI-meting men onderscheid kan maken tussen permeabiliteitsoedeem en cardiaal oedeem. De mate van longoedeem kan worden gemeten door middel van de verdunning van twee tracers in de longcirculatie. Eén tracer blijft intravasculair en een tweede verdeelt zich over zowel het intravasculaire als het interstitiële compartiment. Het verschil tussen de

verdelingsvolumina van beide tracers is een maat voor longoedeem.
Alhoewel bij hart- en vaatchirurgiepatiënten, alsmede bij sepsispatiënten afwijkingen op de thoraxfoto, de aanwezigheid van longoedeem, een verhoogde doorlaatbaarheid van de longvaten en een verstoorde gasuitwisseling zijn aangetoond in eerdere studies, is de precieze bijdrage van longoedeem en endotheelschade aan de thoraxafwijkingen en gasuitwisselingsstoornissen niet goed in kaart gebracht. Daarbij komt dat afwijkingen op de thoraxfoto mede kunnen worden verklaard door bijvoorbeeld atelectase, gekenmerkt door ingeklapte longblaasjes, of de aanwezigheid van een intra-alveolair ontstekingsinfiltraat, zoals bij longontsteking. In beide situaties worden verdichtingen op de foto gezien en is de gasuitwisseling eveneens verstoord.

In het eerste deel van dit proefschrift (hoofdstuk 2 tot en met 4) hebben we de incidentie van en relatie tussen longoedeem, endotheelschade, afwijkingen op de thoraxfoto en een verslechterde gasuitwisseling geëvalueerd bij patiënten met een verhoogd risico op het ontstaan van ARDS: hartchirurgie- en vaatchirurgiepatiënten en sepsispatiënten.

De resultaten van ons onderzoek tonen aan dat bij een groot deel van alle bestudeerde patiënten een verhoogde doorlaatbaarheid wordt gezien van de longvaten, alsmede longoedeem en afwijkingen op de thoraxfoto met een verslechterde gasuitwisseling. Echter, zowel de endotheelschade als de aanwezigheid van longoedeem blijken niet bepalend te zijn voor de verstoorde gasuitwisseling of de radiologische afwijkingen. Met name bij postoperatieve hart- en vaatchirurgiepatiënten (hoofdstuk 2 en 3) speelt atelectase een rol in zowel de radiologische afwijkingen als de verslechterde gasuitwisseling, hetgeen impliceert dat beademingstechnieken om de dichtgeklapte longblaasjes te openen van nut zouden kunnen zijn voor de behandeling van een slechte gasuitwisseling. Bij de patiënten met sepsis is de primaire bron van infectie van belang. In hoofdstuk 4 tonen we aan dat patiënten met sepsis ten gevolge van longontsteking meer verdichtingen op de thoraxfoto hebben, tezamen met meer endotheelschade en een slechtere gasuitwisseling, vergeleken met patiënten die een extrapulmonale bron

van infectie hebben. Atelectase, zoals gevisualiseerd op de röntgenfoto, bleek geen bepalende factor voor verschillen in deze variabelen tussen beide groepen. Dit impliceert dat bij de patiënten met longontsteking het openen van longblaasjes minder effectief zal zijn dan bij de sepsispatiënten met een infectiebron buiten de longen. Dit kan worden verklaard door de aanwezigheid van verdichtingen ten gevolge van directe intra-alveolaire schade met epitheelaantasting en aanwezigheid van een intra-alveolair ontstekingsinfiltraat bij longontsteking. Bij de overige sepsispatiënten leidt mogelijk een systemische ontstekingsreactie tot endotheelschade, met minder directe longschade aan de alveoli. De correlatie van de beademingsparameters met endotheelschade bij sepsispatiënten, met name in geval van longontsteking, betekent dat behandelingen met anti-inflammatoire middelen mogelijk de endotheelschade, en dus de gasuitwisseling en radiologische afwijkingen zouden kunnen verbeteren en dat van beademingsinstellingen minder effect kan worden verwacht. Het ontbreken van enige relatie tussen de gasuitwisseling en de hoeveelheid longoedeem in alle patiëntengroepen betekent dat weinig effect kan worden verwacht van de behandeling van longoedeem door middel van diuretica om de gasuitwisseling te verbeteren.

Nieuwe behandelmethoden om longfalen tegen te gaan, zoals middelen die meer specifiek gericht zijn op het tegengaan van het ontstaan van endotheelschade, alsmede nieuwe beademingstechnieken bij postoperatieve patiënten kunnen in de toekomst worden geëvalueerd.

Tweede deel: Vloeistofbelasting van de intensivecarepatiënt

Op de intensive care worden patiënten onder andere ondersteunend behandeld met betrekking tot hart- en longfunctie. Dit betekent dat naast een optimale instelling van de beademing ook de hartfunctie moet worden geoptimaliseerd. Dit laatste kan door middel van het geven van vulling als het circulerend bloedvolume laag is of het geven van inotropica.

Voor het corrigeren van een laag bloedvolume kunnen uiteenlopende vloeistoffen

worden toegediend. De belangrijkste zijn fysiologische vloeistoffen, zoals bijvoorbeeld fysiologisch zout of de zogenaamde colloïdale vloeistoffen. Colloïdale vloeistoffen kunnen worden onderverdeeld in albumineoplossingen of artificiële oplossingen, zoals gelatine- en zetmeeloplossingen. De vloeistoffen verschillen met betrekking tot de intrinsieke eigenschappen, zoals de concentratie en de halfwaardetijd in het lichaam. Eén van de belangrijkste discussiepunten is het belang van de colloïdaal osmotische druk. Sommige van de vloeistofsoorten, zoals de colloïdale vloeistoffen, kunnen een daling van de colloïdaal osmotische druk van het plasma tegengaan of zelfs verhogen. Een toename van de colloïdaal osmotische druk in het bloed zou kunnen leiden tot een snellere en effectievere toename van het bloedvolume en zou het ontstaan van interstitieel oedeem kunnen tegengaan. In geval van endotheelschade is de doorlaatbaarheid van de bloedvaten echter toegenomen en het belang van de colloïdaal osmotische druk neemt dan af.

Onafhankelijk van de invloed op de colloïdaal osmotische druk, zijn van albumine en zetmeelproducten intrinsieke effecten beschreven op de doorlaatbaarheid van de bloedvaten. Met name tijdens in vitro-experimenten zijn er positieve invloeden van albumine en zetmeelproducten beschreven op de adhesie tussen leukocyten en het endotheel. Bovendien werd een mogelijk mechanische dichting van de poriën in het endotheel beschreven na toediening van zetmeelproducten, zodat de doorlaatbaarheid van de bloedvaten zou verminderen na de infusie van deze vloeistoffen. Bij patiënten zijn deze effecten op de doorlaatbaarheid van bloedvaten tot nu toe echter nauwelijks bestudeerd.

In hoofdstuk 5 hebben we de effecten op korte termijn van vloeistoffen op de hartfunctie bestudeerd bij postoperatieve hart- en vaatchirurgiepatiënten. We hebben gekeken naar de invloed van een zoutoplossing, een gelatineoplossing, een zetmeeloplossing of een albumineoplossing op de vullingsdrukken en intrathoracale bloedvolumina, die bepalend zijn voor de cardiale vulling en uiteindelijk het hartminuutvolume. Patiënten kregen na randomisatie één van de vier verschillende infuusvloeistoffen toegediend. De vier groepen patiënten werden geanalyseerd met betrekking tot hartminuutvolume, cardiale vulling, systemische drukken en

vullingsdrukken. De colloïdale vloeistoffen resulteerden in een significante toename van de colloïdaal osmotische druk, met daarbij een snellere intravasculaire vulling, gemeten als toename van het globaal eind-diastolisch volume (GEDV) en het plasmavolume in vergelijking tot de patiënten die zout kregen toegediend. Bij deze laatste groep patiënten nam de colloïdaal osmotische druk af met een geringere toename van de intravasculaire vulling. De grotere toename van intravasculaire volumina bij patiënten die colloïdale vloeistoffen kregen toegediend resulteerde eveneens in hogere hartminuutvolumina. Tussen de drie colloïdale vloeistoffen onderling werden geen verschillen gevonden.

In hoofdstuk 6 hebben we de effecten van dezelfde vloeistoffen op de longen bestudeerd. Er werd geen effect van de colloïdaal osmotische druk op de hoeveelheid longoedeem gemeten, ondanks een significante toename van de colloïdaal osmotische druk na toediening van colloïdale oplossingen en een afname na toediening van een zoutoplossing. De enige parameter die van invloed bleek op veranderingen in longoedeem was de intravasculaire hydrostatische druk in de longen, gemeten als wiggedruk. We concludeerden dat de hydrostatische druk de belangrijkste determinant van longoedeem is en dat bij lage wiggedrukken de colloïdaal osmotische druk niet van invloed is op de hoeveelheid longoedeem. Los van de invloed van de diverse vloeistoffen op de colloïdaal osmotische druk werd bij de patiëntengroep die een zetmeelproduct kreeg toegediend een daling in de hoeveelheid endotheelschade waargenomen in vergelijking met de groep die een gelatineproduct kreeg toegediend. Dit resultaat zou kunnen betekenen dat zetmeelproducten in vivo inderdaad vaatschade tegengaan.

CURRICULUM VITAE

Joanne Verheij werd geboren op 8 november 1973 in Katwijk. Zij bezocht de middelbare school in Rotterdam, waar zij in 1992 haar diploma gymnasium B behaalde. Vervolgens verhuisde zij naar Brussel, waar zij geneeskunde ging studeren aan de Université Catholique de Louvain (UCL). Zo kon zij haar liefde voor talen en geneeskunde op een uitstekende manier combineren. Tijdens haar studie liep zij verschillende stages, onder andere bij de afdeling inwendige geneeskunde in het Queen Elisabeth Hospital in Birmingham, Engeland. In 1995 behaalde zij haar kandidaatsdiploma en in juni 1999 behaalde zij haar doctoraal, beide 'cum laude' en werd benoemd tot 'docteur en médecine, chirurgie et accouchements'. Vervolgens keerde zij terug naar Nederland, en begon in oktober 1999 met haar promotieonderzoek bij de afdeling Intensive Care aan het VU Medisch Centrum te Amsterdam, hetgeen uitmondde in dit proefschrift. Sinds januari 2004 is zij in opleiding tot klinisch patholoog bij de afdeling Klinische Pathologie van het VU Medisch Centrum.

CURRICULUM VITAE

Joanne Verheij was born 8th November 1973 in Katwijk, the Netherlands. She attended High School (gymnasium B) in Rotterdam, where she graduated in 1992. She moved to Brussels to start medical school at the 'Université Catholique de Louvain' (UCL), thereby combining her interest in languages and medical science. During the seven years of medical studies, she worked in different hospitals. For instance, she did an internship in internal medicine at the Queen Elisabeth Hospital in Birmingham, UK. In 1995, she obtained her 'candidature en sciences médicales' and in 1999 she graduated 'cum laude' as 'docteur en médecine, chirurgie et accouchements'. She returned to the Netherlands in October 1999 and started a research project in the Intensive Care Unit at the Vrije Universiteit Medical Center in Amsterdam, resulting in this thesis. Since January 2004, she works as a specialist trainee in Clinical Pathology at the Vrije Universiteit Medical Center in Amsterdam.

LIST OF PUBLICATIONS

Arif SK, Verheij J, Groeneveld ABJ, Raijmakers PGHM. Hypoproteinemia as a marker of acute respiratory distress syndrome in critically ill patients with pulmonary edema. Intensive Care Med 2002; 28: 310-317

Groeneveld ABJ, Verheij J. Is pulmonary edema associated with a high extravascular thermal volume? Crit Care Med 2004; 32: 899-901

Verheij J, Groeneveld ABJ, Beishuizen A, van Lingen A, Simoons-Smit AM, van Schijndel RJ. Herpes simplex virus type 1 and normal protein permeability in the lungs of critically ill patients: a case for low pathogenicity? Crit Care 2004; 8: R139

Groeneveld ABJ, Breukers RMBGE, Verheij J. Clinical value of intrathoracic volumes from transpulmonary dilution. In: Pinsky MR, Payen D, eds. Functional hemodynamic monitoring. Springer Verlag, Berlin 2004; pp 153-163

Groeneveld ABJ, Verheij J. Methodology and value of assessing extravascular lung water. In: Pinsky MR, Payen D, eds. Functional hemodynamic monitoring. Springer Verlag, Berlin 2004; pp 165-173

De Jager CP, Jessurun ER, Jansen EK, Verheij J, Girbes AR, Strack van Schijndel RJ. Sarcoidosis mimicking ischaemic ventricular arrhythmia and pulmonary embolism. Neth J Med 2005; 63: 70-73

Verheij J, Raijmakers PG, Van Lingen A, Groeneveld ABJ. Simple vs complex radionuclide methods of assessing capillary protein permeability for diagnosing acute respiratory distress syndrome. J Crit Care 2005; 20: 162-171

Verheij J, van Lingen A, Raijmakers PG, Spijkstra JJ, Girbes ARJ, Jansen EK, van den Berg FG, Groeneveld ABJ. Pulmonary abnormalities after cardiac surgery are better explained by atelectasis than by increased permeability oedema. Acta Anaesthesiol Scand 2005; 49: 1302-1310

Verheij J, van Lingen A, Raijmakers PGHM, Rijnsburger ER, Veerman DP, Wisselink W, Girbes ARJ and Groeneveld ABJ. Effect of fluid loading with saline or colloids on pulmonary permeability, oedema and lung injury score after cardiac and major vascular surgery. Br J Anaesth 2005; 96: 21-30

Groeneveld ABJ, Verheij J, van den Berg FG, Wisselink W, Rauwerda JA. Increased pulmonary capillary permeability and extravascular lung water after major vascular surgery: effect on radiography and ventilatory variables? Eur J Anaesthesiol 2006; 23: 36-41

AB Johan Groeneveld and Joanne Verheij. Impaired oxygenation in sepsis-induced acute lung injury and respiratory distress syndrome: effect of increased permeability oedema? Submitted

Verheij J, van Lingen A, Beishuizen A, Christiaans HMT, de Jong JR, Girbes ARJ, Wisselink W, Rauwerda JA, Huybregts MAJM and Groeneveld ABJ. Fluid responsiveness after cardiac or vascular surgery is greater for colloids than for saline. Intensive Care Med 2006; in press

van de Visse E, van der Heijden M, Verheij J, van Nieuw Amerongen GP, van Hinsbergh VWM, Girbes ARJ, Groeneveld ABJ. Effect of prior statin therapy on capillary permeability in the lungs after cardiac or vascular surgery. European Respiratory Journal 2006; in press

J. Verheij, A. van Lingen, J.J. Spijkstra, H. Biermann, A.R.J. Girbes, M. Cuesta, S. Meijer, A.B.J. Groeneveld. Impaired oxygenation and radiographic densities after trauma and surgery are caused by atelectasis rather than increased permeability-oedema. Submitted

AB Johan Groeneveld and Joanne Verheij. Validating extravascular lung water to blood volume ratios in sepsis-induced ALI/ARDS. Submitted

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